

## Methods For The Preparation Of Fused Heterocyclic Succinimide Compounds And Analogs Thereof

This application claims priority from U.S. Application Serial No. 09/885,381,  
5 filed June 20, 2001, which application is incorporated herein by reference in its  
entirety.

### Field of the Invention

The present invention relates to fused cyclic compounds, to methods of using  
10 such compounds in the treatment of nuclear hormone receptor-associated conditions  
such as cancer, and to pharmaceutical compositions containing such compounds.

### Background of the Invention

Nuclear hormone receptors (NHR's) constitute a large super-family of ligand-  
15 dependent and sequence-specific transcription factors. Members of this family  
influence transcription either directly, through specific binding to the promoter target  
genes (Evans, in *Science* **240**: 889-895 (1988)), or indirectly, via protein-protein  
interactions with other transcription factors (Jonat et al., *Cell* **62**: 1189-1204 (1990),  
Schuele et al., *Cell* **62**: 1217-1226 (1990), and Yang-Yen et al., *Cell* **62**: 1205-1215  
20 (1990)). The nuclear hormone receptor super-family (also known in the art as the  
"steroid/thyroid hormone receptor super-family") includes receptors for a variety of  
hydrophobic ligands, including cortisol, aldosterone, estrogen, progesterone,  
testosterone, vitamine D3, thyroid hormone and retinoic acid (Evans, 1988, *supra*).  
In addition to these conventional nuclear hormone receptors, the super-family  
25 contains a number of proteins that have no known ligands, termed orphan nuclear  
hormone receptors (Mangelsdorf et al., *Cell* **83**: 835-839 (1995), O'Malley et al., *Mol.*  
*Endocrinol.* **10**: 1293 (1996), Enmark et al., *Mol. Endocrinol.* **10**, 1293-1307 (1996)  
and Giguere, *Endocrin. Rev.* **20**, 689-725 (1999)). The conventional nuclear hormone  
receptors are generally transactivators in the presence of ligand, and can either be  
30 active repressors or transcriptionally inert in the absence of ligand. Some of the  
orphan receptors behave as if they are transcriptionally inert in the absence of ligand.



Others, however, behave as either constitutive activators or repressors. These orphan nuclear hormone receptors are either under the control of ubiquitous ligands that have not been identified, or do not need to bind ligand to exert these activities.

5           In common with other transcription factors, the nuclear hormone receptors have a modular structure, being comprised of three distinct domains: an N-terminal domain of variable size containing a transcriptional activation function AF-1, a highly conserved DNA binding domain and a moderately conserved ligand-binding domain. The ligand-binding domain is not only responsible for binding the specific ligand but  
10 also contains a transcriptional activation function called AF-2 and a dimerisation domain (Wurtz et al., *Nature Struc. Biol.* **3**, 87-94 (1996), Parker et al., *Nature Struc. Biol.* **3**, 113-115 (1996) and Kumar et al., *Steroids* **64**, 310-319 (1999)). Although the overall protein sequence of these receptors can vary significantly, all share both a common structural arrangement indicative of divergence from an ancestral archetype,  
15 and substantial homology (especially, sequence identity) at the ligand-binding domain.

          The steroid binding nuclear hormone receptors (SB-NHR's) comprise a sub-family of nuclear hormone receptors. These receptors are related in that they share a stronger sequence homology to one another, particularly in the ligand binding domain  
20 (LBD), than to the other members of the NHR super-family (Evans, 1988, *supra*) and they all utilize steroid based ligands. Some examples of this sub-family of NHR's are the androgen receptor (AR), the estrogen receptor (ER), the progesterone receptor (PR), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), the aldosterone receptor (ALDR) and the steroid and xenobiotic receptor (SXR) (Evans *et*  
25 *al.*, WO 99/35246). Based on the strong sequence homology in the LBD, several orphan receptors may also be members of the SB-NHR sub-family.

          Consistent with the high sequence homology found in the LBD for each of the SB-NHR's, the natural ligands for each is derived from a common steroid core. Examples of some of the steroid based ligands utilized by members of the SB-NHR's  
30 include cortisol, aldosterone, estrogen, progesterone, testosterone and dihydrotestosterone. Specificity of a particular steroid based ligand for one SB-NHR versus another is obtained by differential substitution about the steroid core. High

affinity binding to a particular SB-NHR, coupled with high level specificity for that particular SB-NHR, can be achieved with only minor structural changes about the steroid core (e.g., Waller et al., *Toxicol. Appl. Pharmacol.* **137**, 219-227 (1996) and Mekenyan et al., *Environ. Sci. Technol.* **31**, 3702-3711 (1997), binding affinity for  
 5 progesterone towards the androgen receptor as compared to testosterone).

Numerous synthetically derived steroidal and non-steroidal agonists and antagonists have been described for the members of the SB-NHR family. Many of these agonist and antagonist ligands are used clinically in man to treat a variety of medical conditions. RU486 is an example of a synthetic agonist of the PR, which is  
 10 utilized as a birth control agent (Vegeto et al., *Cell* **69**: 703-713 (1992)), and Flutamide is an example of an antagonist of the AR, which is utilized for the treatment of prostate cancer (Neri et al., *Endo.* **91**, 427-437 (1972)). Tamoxifen is an example of a tissues specific modulator of the ER function, that is used in the treatment of breast cancer (Smigel, *J. Natl. Cancer Inst.* **90**, 647-648 (1998)).  
 15 Tamoxifen can function as an antagonist of the ER in breast tissue while acting as an agonist of the ER in bone (Grese et al., *Proc. Natl. Acad. Sci. USA* **94**, 14105-14110 (1997)). Because of the tissue selective effects seen for Tamoxifen, this agent and agents like it are referred to as "partial-agonist" or partial-antagonist". In addition to synthetically derived non-endogenous ligands, non-endogenous ligands for NHR's  
 20 can be obtained from food sources (Regal et al., *Proc. Soc. Exp. Biol. Med.* **223**, 372-378 (2000) and Hempstock et al., *J. Med. Food* **2**, 267-269 (1999)). The flavanoid phytoestrogens are an example of an unnatural ligand for SB-NHR's that are readily obtained from a food source such as soy (Quella et al., *J. Clin. Oncol.* **18**, 1068-1074 (2000) and Banz et al., *J. Med. Food* **2**, 271-273 (1999)). The ability to modulate the  
 25 transcriptional activity of individual NHR by the addition of a small molecule ligand, makes them ideal targets for the development of pharmaceutical agents for a variety of disease states.

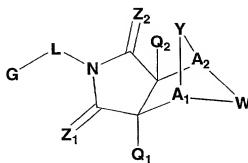
As mentioned above, non-natural ligands can be synthetically engineered to serve as modulators of the function of NHR's. In the case of SB-NHR's, engineering  
 30 of an unnatural ligand can include the identification of a core structure which mimics the natural steroid core system. This can be achieved by random screening against several SB-NHR's or through directed approaches using the available crystal

structures of a variety of NHR ligand binding domains (Bourguet et al., *Nature* **375**, 377-382 (1995), Brzozowski, et al., *Nature* **389**, 753-758 (1997), Shiau et al., *Cell* **95**, 927-937 (1998) and Tanenbaum et al., *Proc. Natl. Acad. Sci. USA* **95**, 5998-6003 (1998)). Differential substitution about such a steroid mimic core can provide agents with selectivity for one receptor versus another. In addition, such modifications can be employed to obtain agents with agonist or antagonist activity for a particular SB-NHR. Differential substitution about the steroid mimic core can result in the formation of a series of high affinity agonists and antagonists with specificity for, for example, ER versus PR versus AR versus GR versus MR. Such an approach of differential substitution has been reported, for example, for quinoline based modulators of steroid NHR in *J. Med. Chem.*, 41, 623 (1999); WO 9749709; US 5696133; US 5696130; US 5696127; US 5693647; US 5693646; US 5688810; US 5688808 and WO 9619458, all incorporated herein by reference.

The compounds of the present invention comprise a core which serves as a steroid mimic, and are useful as modulators of the function of steroid binding nuclear hormone receptors, as well as other NHR as described following.

### Summary of the Invention

The present invention provides fused cyclic compounds of the following formula I and salts thereof, which compounds are especially useful as modulators of nuclear hormone receptor function:



(I)

As used in formula I, and throughout the specification, the symbols have the following meanings unless otherwise indicated, and are, for each occurrence, independently selected:



- G is an aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN, R<sup>1</sup>OC=O, R<sup>1</sup>C=O, R<sup>1</sup>C=S, R<sup>1</sup>HNC=O, R<sup>1</sup>R<sup>2</sup>NC=O, HO-CR<sup>3</sup>R<sup>3'</sup>, nitro, R<sup>1</sup>OCH<sub>2</sub>, R<sup>1</sup>O, NH<sub>2</sub>, NR<sup>4</sup>R<sup>5</sup>, SR<sup>1</sup>, S=OR<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, SO<sub>2</sub>OR<sup>1</sup>, SO<sub>2</sub>NR<sup>1</sup>R<sup>1'</sup>, (R<sup>1</sup>O)(R<sup>1'</sup>O)P=O, oxo, (R<sup>1</sup>)(R<sup>1'</sup>)P=O, or (R<sup>1'</sup>)(NHR<sup>1</sup>)P=O;
- Z<sub>1</sub> is O, S, NH, or NR<sup>6</sup>;  
 Z<sub>2</sub> is O, S, NH, or NR<sup>6</sup>;  
 A<sub>1</sub> is CR<sup>7</sup> or N;  
 A<sub>2</sub> is CR<sup>7</sup> or N;
- Y is J-J'-J'' where J is (CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub> and n = 0-3, J' is a bond or O, S, S=O, SO<sub>2</sub>, NH, NR<sup>7</sup>, C=O, OC=O, NR<sup>1</sup>C=O, CR<sup>7</sup>R<sup>7'</sup>, C=CR<sup>8</sup>R<sup>8'</sup>, R<sup>2</sup>P=O, R<sup>2</sup>P=S, R<sup>2</sup>OP=O, R<sup>2</sup>NHP=O, OP=OOR<sup>2</sup>, OP=ONHR<sup>2</sup>, OP=OR<sup>2</sup>, OSO<sub>2</sub>, C=NR<sup>7</sup>, NHNH, NHNR<sup>6</sup>, NR<sup>6</sup>NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo or aryl or substituted aryl, and J'' is (CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub> and n = 0-3, where Y is not a bond (i.e., if J' is a bond, then in at least one of J or J'' (each defined as (CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub>), n is not zero);
- W is CR<sup>7</sup>R<sup>7'</sup>—CR<sup>7</sup>R<sup>7'</sup>, CR<sup>8</sup>=CR<sup>8'</sup>, CR<sup>7</sup>R<sup>7'</sup>—C=O, NR<sup>9</sup>—CR<sup>7</sup>R<sup>7'</sup>, N=CR<sup>8</sup>, N=N, NR<sup>9</sup>—NR<sup>9'</sup>, S—CR<sup>7</sup>R<sup>7'</sup>, SO—CR<sup>7</sup>R<sup>7'</sup>, SO<sub>2</sub>—CR<sup>7</sup>R<sup>7'</sup>, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W is not NR<sup>9</sup>—CR<sup>7</sup>R<sup>7'</sup>, N=CR<sup>8</sup>, N=N, NR<sup>9</sup>—NR<sup>9'</sup>, S—CR<sup>7</sup>R<sup>7'</sup>, SO—CR<sup>7</sup>R<sup>7'</sup>, SO<sub>2</sub>—CR<sup>7</sup>R<sup>7'</sup>, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO<sub>2</sub>, NH, NR<sup>7</sup>, OC=O, NR<sup>1</sup>C=O, OP=OOR<sup>2</sup>, OP=ONHR<sup>2</sup>, OSO<sub>2</sub>, NHNH, NHNR<sup>6</sup>, NR<sup>6</sup>NH, or N=N;

- Q<sub>1</sub> is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R<sup>1</sup>OC=O, R<sup>4</sup>C=O, R<sup>5</sup>R<sup>6</sup>NC=O, HOCR<sup>7</sup>R<sup>7'</sup>, nitro, R<sup>1</sup>OCH<sub>2</sub>, R<sup>1</sup>O, NH<sub>2</sub>, C=OSR<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup> or NR<sup>4</sup>R<sup>5</sup>;
- Q<sub>2</sub> is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R<sup>1</sup>OC=O, R<sup>4</sup>C=O, R<sup>5</sup>R<sup>6</sup>NC=O, HOCR<sup>7</sup>R<sup>7'</sup>, nitro, R<sup>1</sup>OCH<sub>2</sub>, R<sup>1</sup>O, NH<sub>2</sub>, C=OSR<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup> or NR<sup>4</sup>R<sup>5</sup>;
- L is a bond, (CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub>, NH, NR<sup>5</sup>, NH (CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub>, or NR<sup>5</sup>(CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub>, where n = 0-3; R<sup>1</sup> and R<sup>1'</sup> are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;
- R<sup>2</sup> is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;
- R<sup>3</sup> and R<sup>3'</sup> are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino,  $\text{NR}^1\text{R}^2$ , thiol, alkylthio or substituted alkylthio;

- 5  $\text{R}^4$  is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  $\text{R}^1\text{C}=\text{O}$ ,  $\text{R}^1\text{NHC}=\text{O}$ ,  $\text{SO}_2\text{OR}^1$ , or  $\text{SO}_2\text{NR}^1\text{R}^{1'}$ ;

- $\text{R}^5$  is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  $\text{R}^1\text{C}=\text{O}$ ,  $\text{R}^1\text{NHC}=\text{O}$ ,  $\text{SO}_2\text{R}^1$ ,  $\text{SO}_2\text{OR}^1$ , or  $\text{SO}_2\text{NR}^1\text{R}^{1'}$ ;

- $\text{R}^6$  is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR<sup>1</sup>,  $\text{R}^1\text{C}=\text{O}$ ,  $\text{R}^1\text{NHC}=\text{O}$ ,  $\text{SO}_2\text{R}^1$ ,  $\text{SO}_2\text{OR}^1$ , or  $\text{SO}_2\text{NR}^1\text{R}^{1'}$ ;

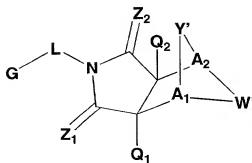
- $\text{R}^7$  and  $\text{R}^{7'}$  are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl,

arylalkyl or substituted arylalkyl, halo, CN, OR<sup>1</sup>, nitro, hydroxylamine, hydroxylamide, amino, NHR<sup>4</sup>, NR<sup>2</sup>R<sup>5</sup>, NOR<sup>1</sup>, thiol, alkylthio or substituted alkylthio, R<sup>1</sup>C=O, R<sup>1</sup>(C=O)O, R<sup>1</sup>OC=O, R<sup>1</sup>NHC=O, SO<sub>2</sub>R<sup>1</sup>, SOR<sup>1</sup>, PO<sub>3</sub>R<sup>1</sup>R<sup>1'</sup>, R<sup>1</sup>R<sup>1'</sup>NC=O, C=OSR<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, SO<sub>2</sub>OR<sup>1</sup>, or SO<sub>2</sub>NR<sup>1</sup>R<sup>1'</sup>, or, wherein A<sub>1</sub> or A<sub>2</sub> contains a group R<sup>7</sup> and W contains a group R<sup>7</sup>, said R<sup>7</sup> groups of A<sub>1</sub> or A<sub>2</sub> and W together form a heterocyclic ring;

R<sup>8</sup> and R<sup>8'</sup> are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR<sup>1</sup>, amino, NHR<sup>4</sup>, NR<sup>2</sup>R<sup>5</sup>, NOR<sup>1</sup>, alkylthio or substituted alkylthio, C=OSR<sup>1</sup>, R<sup>1</sup>OC=O, R<sup>1</sup>C=O, R<sup>1</sup>NHC=O, R<sup>1</sup>R<sup>1'</sup>NC=O, SO<sub>2</sub>OR<sup>1</sup>, S=OR<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, PO<sub>3</sub>R<sup>1</sup>R<sup>1'</sup>, or SO<sub>2</sub>NR<sup>1</sup>R<sup>1'</sup>; and

R<sup>9</sup> and R<sup>9'</sup> are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR<sup>1</sup>, R<sup>1</sup>C=O, R<sup>1</sup>OC=O, R<sup>1</sup>NHC=O, SO<sub>2</sub>R<sup>1</sup>, SO<sub>2</sub>OR<sup>1</sup>, or SO<sub>2</sub>NR<sup>1</sup>R<sup>1'</sup>.  
Compounds within formula I are novel, a preferred subgenus of which is the

following formula Ia:



(Ia)

where G, L, Z<sub>1</sub>, Z<sub>2</sub>, A<sub>1</sub>, A<sub>2</sub>, Q<sub>1</sub> and Q<sub>2</sub> are as defined above;

Y' is J-J'-J'' where J is (CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub> and n = 0-3, J' is a bond or O, S, S=O, SO<sub>2</sub>, NH,

NR<sup>7</sup>, CR<sup>7</sup>R<sup>7'</sup>, R<sup>2</sup>P=O, R<sup>2</sup>P=S, R<sup>2</sup>OP=O, R<sup>2</sup>NHP=O, OP=OOR<sup>2</sup>, OP=ONHR<sup>2</sup>,

5 OSO<sub>2</sub>, NHNH, NHNR<sup>6</sup>, NR<sup>6</sup>NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J'' is (CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub> and n = 0-3, where Y is not a bond; and

W' is CR<sup>7</sup>R<sup>7'</sup>—CR<sup>7</sup>R<sup>7'</sup>, CR<sup>7</sup>R<sup>7'</sup>—C=O, NR<sup>9</sup>—CR<sup>7</sup>R<sup>7'</sup>, N=CR<sup>8</sup>, N=N, NR<sup>9</sup>—NR<sup>9'</sup>,

10 cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein,

when W' is not NR<sup>9</sup>—CR<sup>7</sup>R<sup>7'</sup>, N=CR<sup>8</sup>, N=N, NR<sup>9</sup>—NR<sup>9'</sup>, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO<sub>2</sub>, NH, NR<sup>7</sup>, OP=OOR<sup>2</sup>, OP=ONHR<sup>2</sup>, OSO<sub>2</sub>, NHNH, NHNR<sup>6</sup>, NR<sup>6</sup>NH, or N=N; or alternatively,

Y' is NR<sup>7</sup>—CR<sup>7</sup>R<sup>7'</sup> and W' is CR<sup>8</sup>=CR<sup>8'</sup>; or, alternatively,

15 Y' is CR<sup>7</sup>R<sup>7'</sup>—C=O and W' is NR<sup>9</sup>—CR<sup>7</sup>R<sup>7'</sup>;

where R<sup>2</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>7'</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>9'</sup> are as defined above and with the provisos that

(1) when Y' is -O-, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is -CH<sub>2</sub>-CH<sub>2</sub>-, and A<sub>1</sub> and A<sub>2</sub> are CH, then G-L is not phenyl, monosubstituted phenyl or phenyl which is substituted with two or more of the following groups:

20 methoxy, halo, NO<sub>2</sub>, methyl, CH<sub>3</sub>-S-, OH, CO<sub>2</sub>H, trifluoromethyl, -C(O)-C<sub>6</sub>H<sub>5</sub>, NH<sub>2</sub>, 4-7-epoxy, hexahydro-1H-isoindole-1,3(2H)dione, or -C(O)-CH<sub>3</sub>;

(2) when Y' is -O-, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is CH<sub>2</sub>-CH<sub>2</sub>, and one of A<sub>1</sub> and A<sub>2</sub> is CH and the other is CR<sup>7</sup>, then G-L is not unsubstituted phenyl;

25 (3) when Y' is -O-, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is CH<sub>2</sub>-CH<sub>2</sub>, and one of A<sub>1</sub> and A<sub>2</sub> is CH and the other is C-CH<sub>3</sub>, then G-L is not phenyl substituted with chloro and/or methyl;

(4) when Y' is -O- or -S-, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is CH<sub>2</sub>-CH<sub>2</sub>, and one of A<sub>1</sub> and A<sub>2</sub> is CH and the other is CH or C-alkyl, then G-L is not N-substituted piperazine-alkyl- or N-substituted imidazolidine-alkyl-;

30

- (5) when Y' is -O-; Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is CH<sub>2</sub>-CH<sub>2</sub>, and A<sub>1</sub> and A<sub>2</sub> are CH, then G-L is not oxazole or triazole;
- (6) when Y' is -O-; Q<sub>1</sub> and Q<sub>2</sub> are hydrogen or methyl, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is CH<sub>2</sub>-CH<sub>2</sub>, and A<sub>1</sub> and A<sub>2</sub> are CH or C-CH<sub>3</sub>, then G-L is not thiazole or substituted thiazole (in addition such compounds where G-L is optionally substituted thiadiazole or partially saturated thiazole are optionally removed by proviso where A<sub>1</sub> and A<sub>2</sub> are both CH);
- (7) when Y' contains a group J' selected from S, S=O, SO<sub>2</sub>, NH, NR<sup>7</sup>, R<sup>2</sup>P=O, R<sup>2</sup>P=S, R<sup>2</sup>OP=O, R<sup>2</sup>NHP=O, OP=OOR<sup>2</sup>, OP=ONHR<sup>2</sup>, OSO<sub>2</sub>, NNNH, NHR<sup>6</sup>, NR<sup>6</sup>NH or N=N, W' is CR<sup>7</sup>R<sup>7'</sup>-CR<sup>7</sup>R<sup>7'</sup>, and Z<sub>1</sub> and Z<sub>2</sub> are O, then G-L is not unsubstituted phenyl;
- (8) when Y' is NR<sup>7</sup>, W' is unsubstituted or substituted phenyl, and Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, then Z<sub>1</sub> and Z<sub>2</sub> are not O;
- (9) when Y' is -O-, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is dihydroisoxazole bearing an optionally substituted phenyl group, and A<sub>1</sub> and A<sub>2</sub> are CH, then G-L is not unsubstituted phenyl or dichlorophenyl;
- (10) when Y' is O, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is ethylene oxide, and A<sub>1</sub> and A<sub>2</sub> are CH, then G-L is not methylphenyl or chlorophenyl;
- (11) when Y' is NR<sup>7</sup>-CR<sup>7</sup>R<sup>7'</sup>, W' is CR<sup>8</sup>=CR<sup>8</sup>, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, A<sub>1</sub> and A<sub>2</sub> are CH, C-CH<sub>3</sub>, C-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub> or C-CH<sub>2</sub>-CH<sub>3</sub>, and Z<sub>1</sub> and Z<sub>2</sub> are O, then G-L is not unsubstituted phenyl, monosubstituted phenyl or methylpyridinyl;
- (12) when Y' is CR<sup>7</sup>R<sup>7'</sup>-C=O, W' is NR<sup>9</sup>-CR<sup>7</sup>R<sup>7'</sup>, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, A<sub>1</sub> and A<sub>2</sub> are CH, and Z<sub>1</sub> and Z<sub>2</sub> are O, then G-L is not unsubstituted phenyl;
- (13) when Y' is CHR<sup>7'</sup>-NR<sup>7</sup> where R<sup>7'</sup> is unsubstituted phenyl, methoxy or ethoxy and R<sup>7</sup> is unsubstituted phenyl, methyl or -C(O)-C<sub>6</sub>H<sub>5</sub>, W' is dimethoxyphenylene or unsubstituted phenylene, Z<sub>1</sub> and Z<sub>2</sub> are O, Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, and A<sub>1</sub> and A<sub>2</sub> are CH, C-CN, C-C(O)-C<sub>6</sub>H<sub>5</sub>, or -C(O)-dimethoxyphenyl, then G-L is not unsubstituted phenyl;
- (14) the compound of formula Ia is not 6,10-epithio-4H-thieno-[3',4':5,6]cyclooct[1,2-f]isoindole-7,9(5H,8H)-dione, 8-(3,5-dichlorophenyl)-6,6a,9a,10,11,12,-hexahydro-1,3,6,10-tetramethyl-2,2,13-trioxide, (6R,6aR,9aS,10S);

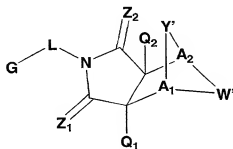
(15) when Y' is O, W' is  $-\text{CH}_2-\text{CH}_2-$ , Q<sub>1</sub> and Q<sub>2</sub> are methyl, Z<sub>1</sub> and Z<sub>2</sub> are O, and A<sub>1</sub> and A<sub>2</sub> are CH, then G-L is not unsubstituted phenyl, phenyl substituted with methoxy, phenyl-alkyl-, or morpholine-alkyl, nor is the compound bridged to itself through a group L which is alkylene to form a bis compound;

(16) when Y' is  $-\text{O}-$ , Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is  $\text{CR}^7\text{R}^{7'}$ - $\text{CR}^7\text{R}^{7'}$ , and A<sub>1</sub> and A<sub>2</sub> are CH, then G-L is not an unsubstituted phenyl group; and

(17) when Y' is  $-\text{O}-$ , Q<sub>1</sub> and Q<sub>2</sub> are hydrogen, Z<sub>1</sub> and Z<sub>2</sub> are O, W' is cyclopentyl, cyclohexyl, 3-phenyl-2-isoxazoline or  $\text{CR}^7\text{R}^{7'}-\text{CR}^7\text{R}^{7'}$  where R<sup>7</sup> and R<sup>7'</sup> are each independently defined as Cl, Br, H and 4-butyrolactone and R<sup>7</sup> and R<sup>7'</sup> are not all simultaneously H, and A<sub>1</sub> and A<sub>2</sub> are CH, then G-L is not an unsubstituted naphthyl ring or a monosubstituted phenyl ring, where said substituent is methoxy, Br, Cl, NO<sub>2</sub>, methyl, ethyl, CH<sub>2</sub>-phenyl, S-phenyl, or O-phenyl.

Preferably, compounds of formula I are monomeric, and are not comprised within other oligomers or polymers.

Another preferred novel subgenus is that of the following formula Ib:



Ib

where G, Z<sub>1</sub>, Z<sub>2</sub>, Q<sub>1</sub> and Q<sub>2</sub> are as defined above;

- 25 Y' is J-J'-J'' where J is  $(\text{CR}^7\text{R}^{7'})_n$  and n = 0-3, J' is a bond or O, S, S=O, SO<sub>2</sub>, NH, NR<sup>7</sup>,  $\text{CR}^7\text{R}^{7'}$ , R<sup>2</sup>P=O, R<sup>2</sup>P=S, R<sup>2</sup>OP=O, R<sup>2</sup>NHP=O, OP=OOR<sup>2</sup>, OP=ONHR<sup>2</sup>, OSO<sub>2</sub>, NNNH, NNNR<sup>6</sup>, NR<sup>6</sup>NH, N=N, cycloalkyl or substituted cycloalkyl,

- cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J'' is  $(CR^7R^{7'})_n$  and  $n = 0-3$ , where Y is not a bond; and W' is  $CR^7R^{7'}-CR^7R^{7'}$ ,  $CR^7R^{7'}-C=O$ ,  $NR^9-CR^7R^{7'}$ ,  $N=CR^8$ ,  $N=N$ ,  $NR^9-NR^9$ , cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein, when W' is not  $NR^9-CR^7R^{7'}$ ,  $N=CR^8$ ,  $N=N$ ,  $NR^9-NR^9$ , or heterocyclo or substituted heterocyclo, then J' must be O, S,  $S=O$ ,  $SO_2$ , NH,  $NR^7$ ,  $OP=OOR^2$ ,  $OP=ONHR^2$ ,  $OSO_2$ ,  $NHNH$ ,  $NHNH^6$ ,  $NR^6NH$ , or  $N=N$ ; or alternatively, Y' is  $CR^7R^{7'}-C=O$  and W' is  $NR^9-CR^7R^{7'}$ ; L is a bond; and  $A_1$  and  $A_2$  are as defined above, especially where  $A_1$  and/or  $A_2$  are alkyl or optionally substituted alkyl (preferred such optional substituents being one or more groups  $V^1$  defined below), with the proviso that, when  $Y' = O$  and  $W' = -CH_2-CH_2-$ , then at least one of  $A_1$  or  $A_2$  is not  $CH$ ; with the further provisos (2), (3), (6), (7) and (8) above.

The compounds of formula I and salts thereof comprise a core which can serve as a steroid mimic (and do not require the presence of a steroid-type (e.g., cyclopentanoperhydrophenanthrene analog) structure).

### Further Description of the Invention

- The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

- The terms "alkyl" and "alk" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms. Exemplary such groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. "Substituted alkyl" refers to an alkyl group substituted with one or more



- substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: halo (e.g., a single halo substituent or multiple halo substituents forming, in the latter case, groups such as a perfluoroalkyl group or an alkyl group bearing  $\text{Cl}_3$  or
- 5  $\text{CF}_3$ ), alkoxy, alkylthio, hydroxy, carboxy (i.e.,  $-\text{COOH}$ ), alkoxyacarbonyl, alkylcarbonyloxy, amino (i.e.,  $-\text{NH}_2$ ), carbamoyl or substituted carbomoyl, carbamate or substituted carbamate, urea or substituted urea, amidinyl or substituted amidinyl, thiol (i.e.,  $-\text{SH}$ ), aryl, heterocycle, cycloalkyl, heterocycloalkyl,  $-\text{S}$ -aryl,  $-\text{S}$ -heterocycle,  $-\text{S}=\text{O}$ -aryl,  $-\text{S}=\text{O}$ -heterocycle, arylalkyl-O-,
  - 10  $-\text{S}(\text{O})_2$ -aryl,  $-\text{S}(\text{O})_2$ -heterocycle,  $-\text{NHS}(\text{O})_2$ -aryl,  $-\text{NHS}(\text{O})_2$ -heterocycle,  $-\text{NHS}(\text{O})_2\text{NH}$ -aryl,  $-\text{NHS}(\text{O})_2\text{NH}$ -heterocycle,  $-\text{P}(\text{O})_2$ -aryl,  $-\text{P}(\text{O})_2$ -heterocycle,  $-\text{NHP}(\text{O})_2$ -aryl,  $-\text{NHP}(\text{O})_2$ -heterocycle,  $-\text{NHP}(\text{O})_2\text{NH}$ -aryl,  $-\text{NHP}(\text{O})_2\text{NH}$ -heterocycle,  $-\text{O}$ -aryl,  $-\text{O}$ -heterocycle,  $-\text{NH}$ -aryl,  $-\text{NH}$ -heterocycle,  $-\text{NHC}=\text{O}$ -aryl,  $-\text{NHC}=\text{O}$ -alkyl,  $-\text{NHC}=\text{O}$ -heterocycle,  $-\text{OC}=\text{O}$ -aryl,  $-\text{OC}=\text{O}$ -heterocycle,  $-\text{NHC}=\text{ONH}$ -aryl,
  - 15  $-\text{NHC}=\text{ONH}$ -heterocycle,  $-\text{OC}=\text{OO}$ -aryl,  $-\text{OC}=\text{OO}$ -heterocycle,  $-\text{OC}=\text{ONH}$ -aryl,  $-\text{OC}=\text{ONH}$ -heterocycle,  $-\text{NHC}=\text{OO}$ -aryl,  $-\text{NHC}=\text{OO}$ -heterocycle,  $-\text{NHC}=\text{OO}$ -alkyl,  $-\text{C}=\text{ONH}$ -aryl,  $-\text{C}=\text{ONH}$ -heterocycle,  $-\text{C}=\text{OO}$ -aryl,  $-\text{C}=\text{OO}$ -heterocycle,  $-\text{N}(\text{alkyl})\text{S}(\text{O})_2$ -aryl,  $-\text{N}(\text{alkyl})\text{S}(\text{O})_2$ -heterocycle,  $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{NH}$ -aryl,  $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{NH}$ -heterocycle,  $-\text{N}(\text{alkyl})\text{P}(\text{O})_2$ -aryl,  $-\text{N}(\text{alkyl})\text{P}(\text{O})_2$ -heterocycle,
  - 20  $-\text{N}(\text{alkyl})\text{P}(\text{O})_2\text{NH}$ -aryl,  $-\text{N}(\text{alkyl})\text{P}(\text{O})_2\text{NH}$ -heterocycle,  $-\text{N}(\text{alkyl})$ -aryl,  $-\text{N}(\text{alkyl})$ -heterocycle,  $-\text{N}(\text{alkyl})\text{C}=\text{O}$ -aryl,  $-\text{N}(\text{alkyl})\text{C}=\text{O}$ -heterocycle,  $-\text{N}(\text{alkyl})\text{C}=\text{ONH}$ -aryl,  $-\text{N}(\text{alkyl})\text{C}=\text{ONH}$ -heterocycle,  $-\text{OC}=\text{ON}(\text{alkyl})$ -aryl,  $-\text{OC}=\text{ON}(\text{alkyl})$ -heterocycle,  $-\text{N}(\text{alkyl})\text{C}=\text{OO}$ -aryl,  $-\text{N}(\text{alkyl})\text{C}=\text{OO}$ -heterocycle,  $-\text{C}=\text{ON}(\text{alkyl})$ -aryl,  $-\text{C}=\text{ON}(\text{alkyl})$ -heterocycle,  $-\text{NHS}(\text{O})_2\text{N}(\text{alkyl})$ -aryl,  $-\text{NHS}(\text{O})_2\text{N}(\text{alkyl})$ -heterocycle,
  - 25  $-\text{NHP}(\text{O})_2\text{N}(\text{alkyl})$ -aryl,  $-\text{NHP}(\text{O})_2\text{N}(\text{alkyl})$ -heterocycle,  $-\text{NHC}=\text{ON}(\text{alkyl})$ -aryl,  $-\text{NHC}=\text{ON}(\text{alkyl})$ -heterocycle,  $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{N}(\text{alkyl})$ -aryl,  $-\text{N}(\text{alkyl})\text{S}(\text{O})_2\text{N}(\text{alkyl})$ -heterocycle,  $-\text{N}(\text{alkyl})\text{P}(\text{O})_2\text{N}(\text{alkyl})$ -aryl,  $-\text{N}(\text{alkyl})\text{P}(\text{O})_2\text{N}(\text{alkyl})$ -heterocycle,  $-\text{N}(\text{alkyl})\text{C}=\text{ON}(\text{alkyl})$ -aryl, and  $-\text{N}(\text{alkyl})\text{C}=\text{ON}(\text{alkyl})$ -heterocycle. In the aforementioned exemplary substituents, in
  - 30 each instance, groups such as "alkyl", "aryl" and "heterocycle" can themselves be optionally substituted; for example, "alkyl" in the group "NCH=OO-alkyl" recited

above can be optionally substituted so that both "NHC=OO-alkyl" and "NHC=OO-substituted alkyl" are exemplary substituents. Exemplary alkyl substituents also include groups such as "T" and "T-R<sup>12</sup>" (which are defined below), especially for substituted alkyl groups within A<sub>1</sub> or A<sub>2</sub>.

- 5       The term "alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond. Exemplary such groups include ethenyl or allyl. "Substituted alkenyl" refers to an alkenyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not
- 10       limited to, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents.

- The term "alkynyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. Exemplary such groups include ethynyl. "Substituted alkynyl" refers to an alkynyl
- 15       group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents.

- The term "cycloalkyl" refers to a fully saturated cyclic hydrocarbon group
- 20       containing from 1 to 4 rings and 3 to 8 carbons per ring. Exemplary such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, nitro, cyano, alkyl or substituted alkyl, as
- 25       well as those groups recited above as exemplary alkyl substituents, and as previously mentioned as preferred aryl substituents in the definition for G. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially cycloalkenyl or substituted cycloalkenyl.

- The term "cycloalkenyl" refers to a partially unsaturated cyclic hydrocarbon
- 30       group containing 1 to 4 rings and 3 to 8 carbons per ring. Exemplary such groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, etc. "Substituted cycloalkenyl" refers to a cycloalkenyl group substituted with one more substituents, preferably 1 to 4

substituents, at any available point of attachment. Exemplary substituents include but are not limited to nitro, cyano, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents, and as previously mentioned as preferred aryl substituents in the definition for G. Exemplary substituents also include

5 spiro-attached or fused cyclic substituents, especially cycloalkyl or substituted cycloalkyl.

The terms "alkoxy" or "alkylthio" refer to an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively. The terms "substituted alkoxy" or "substituted alkylthio" refer to a substituted alkyl group

10 as described above bonded through an oxygen or sulfur linkage, respectively.

The term "alkoxycarbonyl" refers to an alkoxy group bonded through a carbonyl group.

The term "alkylcarbonyl" refers to an alkyl group bonded through a carbonyl group. The term "alkylcarbonyloxy" refers to an alkylcarbonyl group bonded through

15 an oxygen linkage.

The terms "arylalkyl", "substituted arylalkyl," "cycloalkylalkyl," "substituted cycloalkylalkyl," "cycloalkenylalkyl", "substituted cycloalkenylalkyl", "heterocycloalkyl" and "substituted heterocycloalkyl" refer to aryl, cycloalkyl, cycloalkenyl and heterocyclo groups bonded through an alkyl group, substituted on

20 the aryl, cycloalkyl, cycloalkenyl or heterocyclo and/or the alkyl group where indicated as "substituted."

The term "aryl" refers to cyclic, aromatic hydrocarbon groups which have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two or more aromatic rings (bicyclic, etc.), the aromatic

25 rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl, phenanthrenyl and the like). "Substituted aryl" refers to an aryl group substituted by one or more substituents, preferably 1,2,3,4 or 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, nitro, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, cyano,

30 alkyl-S(O)<sub>m</sub> (m=0, 1 or 2), alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents and as previously mentioned as preferred aryl substituents in the definition for G. Exemplary substituents also include fused cyclic

substituents, such as heterocyclo or cycloalkenyl, or substituted heterocyclo or cycloalkenyl, groups (e.g., thereby forming a fluoroenyl, tetrahydronaphthalenyl, or dihydroindenyl group).

- “Carbamoyl” refers to the group  $\text{-CONH-}$  which is bonded on one end to the remainder of the molecule and on the other to hydrogen or an organic moiety (such as alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, alkylcarbonyl, hydroxyl and substituted nitrogen). “Carbamate” refers to the group  $\text{-O-CO-NH-}$  which is bonded on one end to the remainder of the molecule and on the other to hydrogen or an organic moiety (such as those listed above). “Urea” refers to the group  $\text{-NH-CO-NH-}$  which is bonded on one end to the remainder of the molecule and on the other to hydrogen or an organic moiety (such as those listed above). “AmidinyI” refers to the group  $\text{-C(=NH)(NH}_2\text{)}$ . “Substituted carbamoyl,” “substituted carbamate,” “substituted urea” and “substituted amidinyI” refer to carbamoyl, carbamate, urea or amidinyI groups as described above in which one more of the hydrogen groups are replaced by an organic moiety (such as those listed above).

- The terms “heterocycle”, “heterocyclic” and “heterocyclo” refer to fully saturated, or partially or fully unsaturated, including aromatic (i.e., “heteroaryl”) cyclic groups (for example, 3 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. (The term “heteroarylium” refers to a heteroaryl group bearing a quaternary nitrogen atom and thus a positive charge.) The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. Exemplary monocyclic heterocyclic groups include ethylene oxide, azetidinyI, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, hexahydrodiazepinyl, 4-piperidinyl, pyridyl, pyrazinyl, pyrimidinyl,

- pyridazinyl, triazinyl, triazolyl, tetrazolyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl,
- 5 benzoxadiazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofurazanyl, chromonyl, coumarinyl, benzopyranyl, cinnolynyl, quinoxalynyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydrobenzodioxinyl, dihydrodioxidobenzothiophenyl,
- 10 dihydroisoindolyl, dihydroindolyl, dihydroquinolinyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), triazinylazepinyl, tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.
- “Substituted heterocycle,” “substituted heterocyclic,” and “substituted
- 15 heterocycle” (such as “substituted heteroaryl”) refer to heterocycle, heterocyclic or heterocycle groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, nitro, oxo (i.e., = O), cyano, alkyl-S(O)<sub>m</sub>- (m = 0, 1 or 2), alkyl or
- 20 substituted alkyl, as well as those groups recited above as exemplary alkyl substituents, and as previously mentioned as preferred heterocycle substituents in the definition for G.

- The term “quaternary nitrogen” refers to a tetravalent positively charged nitrogen atom including, for example, the positively charged nitrogen in a
- 25 tetraalkylammonium group (e.g., tetramethylammonium, N-methylpyridinium), the positively charged nitrogen in protonated ammonium species (e.g., trimethylhydroammonium, N-hydropyridinium), the positively charged nitrogen in amine N-oxides (e.g., N-methyl-morpholine-N-oxide, pyridine-N-oxide), and the positively charged nitrogen in an N-amino-ammonium group (e.g., N-aminopyridinium).

- 30 The terms “halogen” or “halo” refer to chlorine, bromine, fluorine or iodine.

The terms “hydroxylamine” and “hydroxylamide” refer to the groups OH-NH- and OH-NH-CO-, respectively.

When a functional group is termed "protected", this means that the group is in modified form to mitigate, especially preclude, undesired side reactions at the protected site. Suitable protecting groups for the methods and compounds described herein include, without limitation, those described in standard textbooks, such as

- 5 Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

When a term such as "(CRR)n" is used, it denotes an optionally substituted alkyl chain existing between the two fragments to which it is bonded, the length of which chain is defined by the range described for the term n. An example of this is n=0-3, implying from zero to three (CRR) units existing between the two fragments, 10 which are attached to the primary and terminal (CRR) units. In the situation where the term n is set to zero (n = 0) then a bond exists between the two fragments attached to (CRR).

Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

- 15 Divalent groups, such as those in the definition of W (e.g.,  $\text{NR}^9\text{-CR}^7\text{R}^7$ ), may be bonded in either direction to the remainder of the molecule (e.g.,  $\text{-}\underset{\text{I}}{\text{A}}_1\text{-NR}^9\text{-CR}^7\text{R}^7\text{-}\underset{\text{I}}{\text{A}}_2\text{-}$  or,  $\text{-}\underset{\text{I}}{\text{A}}_1\text{-CR}^7\text{R}^7\text{-NR}^9\text{-}\underset{\text{I}}{\text{A}}_2\text{-}$  for the aforementioned group within the definition of W).

Carboxylate anion refers to a negatively charged group  $\text{-COO}^-$ .

- 20 The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of formula I contains both a basic moiety, 25 such as but not limited to a pyridine or imidazole, and an acidic moiety such as but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolation or purification steps which may be employed during 30 preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount,

in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of formula I which contain a basic moiety, such as but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, hydroxyethanesulfonates (e.g., 2-hydroxyethanesulfonates), lactates, maleates, methanesulfonates, naphthalenesulfonates (e.g., 2-naphthalenesulfonates), nicotines, nitrates, oxalates, pectinates, persulfates, phenylpropionates (e.g., 3-phenylpropionates), phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

The compounds of formula I which contain an acidic moiety, such but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glycamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug" as employed herein denotes a compound

which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof. Solvates of the compounds of formula I include, for example, hydrates.

Compounds of the formula I, and salts thereof, may exist in their tautomeric  
5 form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers of the present compounds (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric

- forms and diastereomeric forms, are contemplated within the scope of this invention.
- 10 Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers (e.g., as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration as defined by the IUPAC 1974 Recommendations.
- 15 The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active
- 20 acid followed by crystallization.

- All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both cis (*Z*) and trans (*E*) alkene isomers, as well as cis and trans isomers of cyclic hydrocarbon or heterocyclic
- 25 rings. In certain cases, for example, the exo or endo conformation can be preferred for the fused ring system bonded to G-L in formula I. For example, for androgen receptor antagonists (or selective androgen receptor modulators), where Y is O or NR<sup>7</sup>, the exo configuration can be preferred, while for most other definitions of Y, the endo configuration can be preferred. As can be appreciated, the preferred
- 30 configuration can be a function of the particular compound and its preferred activity. Separation of configurational isomers can be achieved by any suitable method, such as column chromatography.



Throughout the specifications, groups and substituents thereof may be chosen to provide stable moieties and compounds.

Embodiments indicated herein as exemplary or preferred are intended to be illustrative and not limiting.

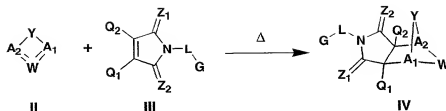
### Methods of Preparation

- The compounds of the present invention may be prepared by methods such as those illustrated in the following Schemes I to XI. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. Combinatorial techniques may be employed in the preparation of compounds, for example, where the intermediates possess groups suitable for these techniques. See the following which describe other methods which may be employed in the preparation of compounds of the present invention: Li, *et al.*, *Eur. J. Org. Chem.* **9**, 1841-1850 (1998); Li, Y-Q, *Synlett.* **5**, 461-464 (1996); Thiemann, *et al.*, *Bull. Chem. Soc. Jpn.* **67**, 1886-1893 (1994); Tsuge *et al.*, *Heterocycles* **14**, 423-428 (1980); Ward *et al.*, *Can J. Chem.* **75**, 681-693 (1997); Ward *et al.*, *Can J. Chem.* **69**, 1487-1497 (1991); Ward *et al.*, *Tetrahedron Lett.* **31**, 845-848 (1990); Fleming *et al.*, *J. Org. Chem.* **44**, 2280-2282 (1979); Jankowski *et al.*, *J. Organomet. Chem.* **595**, 109-113 (2000); Keglevich *et al.*, *J. Organomet. Chem.* **579**, 182-189 (1999); Keglevich *et al.*, *J. Organomet. Chem.* **570**, 49-539 (1998); Jankowski *et al.*, *Hetroat. Chem.* **7**, 369-374 (1996); Jankowski *et al.*, *J. Am. Chem. Soc.* **113**, 7011-7017 (1991); Quin *et al.*, *Tetrahedron Lett.* **31**, 6473-6476 (1990); Quin *et al.*, *J. Org. Chem.* **59**, 120-129 (1994); Quin *et al.*, *J. Org. Chem.* **58**, 6212-6216 (1993); Quin *et al.*, *Phosphorous, Sulfur Silicon Relat. Elem.* **63**, 349-362 (1991); Quin *et al.*, *Hetroat. Chem.* **2**, 359-367 (1991); Hussong *et al.*, *Phosphorus Sulfur.* **25**, 201-212 (1985); Quin *et al.*, *J. Org. Chem.* **51**, 3341-3347 (1986); Myers *et al.*, *J. Am. Chem. Soc.* **114**, 5684-5692 (1992); Myers *et al.*, *J. Am. Chem. Soc.* **113**, 6682-6683 (1991); Shen *et al.*, US Patent No. 5817679; Cordone *et al.*, *J. Am. Chem. Soc.* **111**, 5969-5970 (1989); Jung *et al.*, *J. Chem. Soc. Commun.* 630-632 (1984); Lay *et al.*, *J. Am. Chem. Soc.* **104**, 7658-7659 (1982); Gonzalez *et al.*, *J. Am. Chem. Soc.* **117**, 3405-3421 (1995); Kreher *et al.*, *Chem Ber.* **125**, 183-189 (1992); Simig *et al.*, *Synlett.* **7**, 425-426 (1990); Sha *et al.*, *J. Org. Chem.* **55**, 2446-2450 (1990); Drew *et al.*, *J. Chem. Soc., Perkin Trans. I* **7**, 1277-1284 (1985); Kreher *et al.*, *Anorg. Chem., Org Chem.* **31B**, 599-604 (1976); Avalos *et al.*, *Tetrahedron Lett.* **39**, 9301-9304 (1998); Gousse *et al.*, *Macromolecules* **31**, 314-321 (1998); Mikhailychenko *et*

- al., *Khim. Geterotsikl. Soedin.* **6**, 751-758 (1993); Lubowitz *et al.*, US Patent No. 4476184; Padwa *et al.*, *J. Org. Chem.* **61**, 3706-3714 (1996); Schlessinger *et al.*, *J. Org. Chem.* **59**, 3246-3247 (1994); Buchmeiser *et al.*, WO Publication No. 9827423; Tanabe *et al.*, Japanese Patent Document JP 07144477; Mochizuki *et al.*, Japanese Patent Document JP 63170383; Hosoda *et al.*, Japanese Patent Document JP 62053963; Onaka *et al.*, Japanese Patent Document JP 62053964; Kato *et al.*, Japanese Patent Document JP 53086035; Kato *et al.*, Japanese Patent Document JP 51088631; Tottori *et al.*, Japanese Patent Document JP 49124225; Augustin *et al.*, German Patent Document DD101271; Title *et al.*, French Patent Document FR 2031538; Gousse *et al.*, *Polym. Int.* **48**, 723-731 (1999); Padwa *et al.*, *J. Org. Chem.* **62**, 4088-4096 (1997); Theurillat-Moritz *et al.*, *Tetrahedron: Asymmetry* **7**, 3163-3168 (1996); Mathews *et al.*, *J. Carbohydr. Chem.* **14**, 287-97 (1995); Srivastava *et al.*, *Natl. Acad. Sci. Lett. (India)* **15**, 41-44 (1992); Mayorga *et al.*, *Rev. Cubana Quim.* **4**, 1-6 (1988); Kondoli *et al.*, *J. Chem. Res., Synop.* **3**, 76 (1987); Primelles *et al.*, *Cent. Azucar* 7-14 (1985); Solov'eva *et al.*, *Khim. Geterotsikl. Soedin.* **5**, 613-15 (1984); Liu *et al.*, *Yaoxue Xuebao* **18**, 752-759 (1983); Joshi *et al.*, *Indian J. Chem., Sect. B.* **22B**, 131-135 (1983); Amos *et al.*, WO Publication No. 9829495; Odagiri *et al.*, US Patent No. 4670536; Gallucci *et al.*, European Patent Document EP 355435; Redmore, D. US Patent No. 3821232; Nakano *et al.*, *Heterocycles* **35**, 37-40 (1993); Tomisawa *et al.*, *Chem. Pharm. Bull.* **36**, 1692-1697 (1988); Krow *et al.*, *J. Heterocycl. Chem.* **22**, 131-135 (1985); Krow *et al.*, *J. Org. Chem.* **47**, 1989-1993 (1982); Liu *et al.*, *Yaoxue Xuebao* **18**, 752-759 (1983); Nishikawa *et al.*, *Yaoxue Xuebao* JP 01061457; and/or Rice *et al.*, *J. Med. Chem.* **11**, 183-185 (1968).

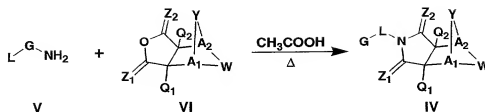
- All documents cited in the present specification, such as those cited in this
- 25 "Methods of Preparation" as well as other sections herein, are incorporated herein by reference in their entirety. Reference to any document herein is not to be construed as an admission that such document is prior art.

Scheme I



- As illustrated in Scheme I, a diene of formula **II** can be reacted with a dienophile of formula **III**, under conditions readily selected by one skilled in the art (such as by the addition of heat ("Δ")), to obtain a compound of formula **IV**, which is a compound of formula I. An intermediate diene of formula **II** can be obtained from commercial sources or readily made by one skilled in the art, for example, in accordance with the following literature documents and the references found therein: Hofman *et al.*, *J. Agric. Food Chem.* **45**, 898-906 (1997); Baciocchi *et al.*, *J. Chem. Soc., Perkin Trans. 2* **8**, 821-824 (1975); Wu *et al.*, *J. Heterocycles* **38**, 1507-1518 (1994); Yin *et al.*, *Tetrahedron Lett.* **38**, 5953-5954 (1997); Mic'ovic' *et al.*, *Tetrahedron* **20**, 2279-2287 (1964); Gorbunova *et al.*, *J. Org. Chem.* **35**, 1557-1566 (1999); Rassu *et al.*, *Chem. Soc. Rev.* **29**, 109-118 (2000); Kabardin *et al.*, *Russ. Chem. Rev.* **68**, 765-779 (1999); Barluenga *et al.*, *Aldrichimica Acta* **32**, 4-15 (1999); Bogdanowicz-Szwed *et al.*, *Pol. Wiad. Chem.* **52**, 821-842 (1998); Casiraghi *et al.*, *Adv. Asymmetric Synth.* **3**, 113-189 (1998); and/or Baeckvall *et al.*, *Chem. Rev.* **98**, 2291-2312 (1998). An intermediate dieneophile of formula **III** can be obtained from commercial sources or readily made by one skilled in the art, for example, in accordance with the following literature references and the references found therein: Deshpande *et al.*, *Heterocycles* **51**, 2159-2162 (1999); Seijas *et al.*, *J. Chem. Res., Synop.* **7**, 420-421 (1999); Langer *et al.*, *Eur. J. Org. Chem.* **7**, 1467-1470 (1998); Kita *et al.*, Japanese Patent Document JP 09194458; Lopez-Alvarado *et al.*, *J. Org. Chem.* **61**, 5865-5870 (1996); Condon *et al.*, US Patent No. 5523277; Sasaki-hara *et al.*, Japanese Patent Document JP 04290868; Igarashi *et al.*, Japanese Patent Document JP 04149173; Aoyama *et al.*, Japanese Patent Document JP 04134063; Aoyama *et al.*, Japanese Patent Document JP 04134062; Pastor *et al.*, *J. Org. Chem.* **53**, 5776-5779 (1988); and/or Takahashi *et al.*, *Chem. Lett.* **6**, 1229-1232 (1987).

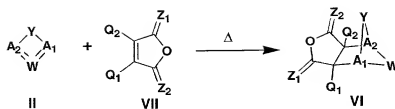
## Scheme II



- As illustrated in Scheme II, compounds of formula I can be obtained by reaction of a primary amine of formula V with a substituted anhydride-like intermediate of formula VI, for example, in a solvent such as acetic acid with or without heating, to yield a compound of formula IV, which is a compound of formula I. Primary amines of formula V can be obtained from commercial sources or readily synthesized by one skilled in the art. Anhydride-like agents of formula VI can be obtained from commercial sources or readily synthesized by one skilled in the art. The documents listed following describe exemplary approaches for the synthesis of intermediates of formula VI as well as synthetic approaches which can be applied to the synthesis of compounds of formula IV (all incorporated herein by reference in their entirety): Kohler, E. P.; Tishler, M.; Potter, H.; Thompson, H. T. *J. Am. Chem. Soc.* 1939, 1057-1061; Yur'ev, Y. K.; Zefirov, N. S. *J. Gen. Chem. U.S.S.R. (Engl. Transl.)* 1961, 31, 772-5; Norman G. Gaylord US Patent No. 3,995,099; Schueler, P. E.; Rhodes, Y. E. *J. Org. Chem.* 1974, 39, 2063-9; Ishitobi, H.; Tanida, H; Tsuji, T. *Bull. Chem. Soc. Japan* 1971, 44, 2993-3000; Stájer, G.; Virág, M.; Szabó, A. E.; Bernáth, G.; Sohár, P.; Sillanpää, R. *Acta. Chem. Scand.* 1996, 50, 922-30; Hart, H.; Ghosh, T. *Tetrahedron Lett.* 1988, 29, 881-884; Kato, M.; Yamamoto, S.; Yoshihara, T.; Furuichi, K.; Miwa, T. *Chem. Lett.* 1987, 1823-1826; Kottwitz, J.; Vorbrüggen, H. *Synthesis* 1995, 636-637; Creary, X. *J. Org. Chem.* 1975, 40, 3326-3331; Alder, K.; Ache, H.-J.; Flock, F. H. *Chem. Ber.* 1960, 93, 1888-1895; Toder, B. H.; Branca, S. J.; Dieter, R. K.; Smith, A. B. III *Synth. Commun.* 1975, 5, 435-439; Sprague, P. W.; Heikes, J. E.; Gougoutas, J. Z.; Malley, M. F.; Harris, D. N.; and/or Greenberg, R. J. *Med. Chem.* 1985, 28, 1580-1590.

The aforementioned approach(es) can be applied in a combinatorial fashion, for example, by utilizing a multi-well reaction block such as is described in Waldemar Ruediger, Wen-Jeng Li, John W., Allen Jr., and Harold N. Weller III, US Patent No. 5,961,925, Apparatus for Synthesis of Multiple Organic Compounds With Pinch Valve Block (incorporated herein by reference in its entirety). By utilizing the above-mentioned multi-well reaction block, one can, for example, perform multiples of 96 reactions at a time. Solvent can then be removed from the reaction tubes without removal from the reaction block and the crude products can be precipitated using a base such as sodium bicarbonate. The precipitates can be collected by filtration of the reaction block and then the desired products can be transferred directly to 96 well plates for screening. In this fashion, a large array of compounds of formula **I** can be synthesized, and tests conducted as desired by an automated approach.

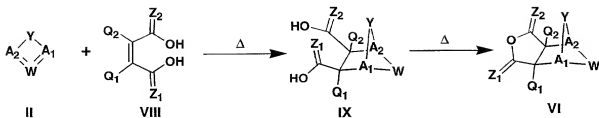
## Scheme III



- 5                Scheme **III** describes a method for preparing an intermediate compound of formula **VI** which can be used to synthesize a compound of formula **I**, as described in Scheme **II**. As described in Scheme **III**, a diene of formula **II** can be reacted with a dieneophile of formula **VII** to yield the intermediate of formula **VI**. The methods applied to obtain such a transformation are analogous to those described in Scheme **I**.

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Scheme IV



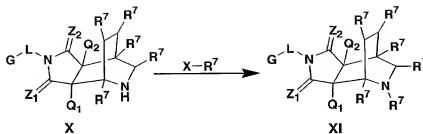
- Scheme **IV** describes a method for preparing an intermediate compound of formula **VI** which can be used to synthesize a compound of formula **I**, as described in Scheme **II**. As shown in Scheme **IV**, a diene of formula **II** can be reacted with a dieneophile of formula **VIII** to yield the intermediate of formula **IX**. The intermediate of formula **IX** can be dehydrated to an anhydride-like intermediate of formula **VI**. Dehydration of the bis-acid intermediate of formula **IX** can be achieved by a variety of methods, such as those known to one skilled in the art and described in the following documents and the references embodied therein: Sprague *et al.*, *J. Med. Chem.* **28**, 1580-1590 (1985); and/or Retemi *et al.*, *J. Org. Chem.* **61**, 6296-6301 (1996).



- Schemes I to IV describe general methods for the synthesis of compounds of formula I, and intermediates thereof, in which substitution about the ring system is incorporated directly, for example, at the level of the intermediate diene, dienophile, anhydride-like intermediate and amine groups. In addition to these approaches,
- 5 additional substitution can be incorporated onto an already-prepared compound of formula I by a variety of approaches to prepare other compounds of the formula I. Exemplary methods for further substitution are described in Schemes V to XI.

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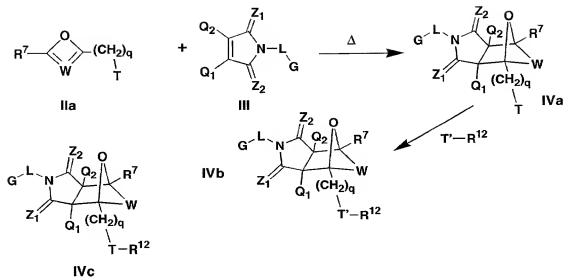
Scheme V



- Scheme V describes one such approach to incorporating additional substitution into a structure of formula I. As illustrated in Scheme V, a compound of formula X, which is a compound of formula I where  $A_1$  and  $A_2$  are  $\text{CR}^7$ , W is  $\text{NH}-\text{CHR}^7$  and Y is  $\text{CHR}^7-\text{CHR}^7$ , can be functionalized at the free amine of the group W by reaction with any of a variety of electrophilic agents such as acid halides or alkyl halides in the presence of base, for example, by methods known by one skilled in the art. In Scheme V, X is a leaving group, and a compound of formula XI is a compound of formula I where  $A_1$  and  $A_2$  are  $\text{CR}^7$ , W is  $\text{NR}^7-\text{CHR}^7$  and Y is  $\text{CHR}^7-\text{CHR}^7$ .

5 substitution onto a compound of formula **I**. As illustrated in Scheme **VI**, a compound of formula **XII**, which is a compound of formula **I** where  $A_1$  and  $A_2$  are  $CR^7$ ,  $W$  is  $S-CHR^7$  and  $Y$  is  $CHR^7-CHR^7$ , can be partially oxidized with an oxidizing agent such as mCPBA or other agents such as those known to one skilled in the art, to give the sulfoxide analog of formula **XIII**, which is a compound of formula **I** where  $A_1$  and  $A_2$  are  $CR^7$ ,  $W$  is  $SO-CHR^7$  and  $Y$  is  $CHR^7-CHR^7$ . Further treatment of a compound of formula **XIII** with an oxidizing agent such as mCPBA or other agents such as those known to one skilled in the art, can yield the sulphone analog of formula **XIV**, which is a compound of formula **I** where  $A_1$  and  $A_2$  are  $CR^7$ ,  $W$  is  $SO_2-CHR^7$  and  $Y$  is  $CHR^7-CHR^7$ . Alternatively, a compound of formula **XII** can be converted  
15 directly to a compound of formula **XIV** by prolonged treatment with an oxidizing agent, such as mCPBA, or with other agents such as those known to one skilled in the art.

## Scheme VII



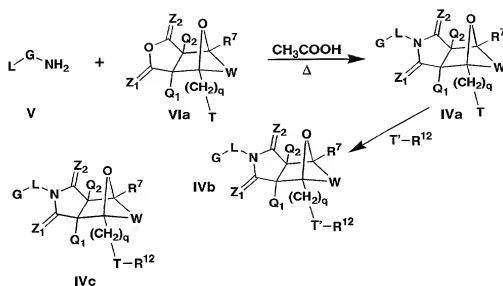
Scheme VII describes another approach to incorporating additional substitution onto a compound of formula I. As illustrated in Scheme VII, a diene of formula IIa can be reacted with a dienophile of formula III, as described in Scheme I, to yield a compound of formula IVa, which is a compound of formula I where Y is O,  $A_2$  is  $CR^7$  and  $A_1$  is  $C-(CH_2)_q-T$ . The compound of formula IVa can be reacted with a reagent of formula  $R^{12}-T'$  to obtain a compound of formula IVb or IVc which are compounds of formula I where Y is O,  $A_2$  is  $CR^7$  and  $A_1$  is  $C-(CH_2)_q-T'-R^{12}$  or  $C-(CH_2)_q-T-R^{12}$ , respectively. The reagent  $R^{12}-T'$  can be obtained from commercial sources or can readily be prepared by one skilled in the art.

In the above Scheme,  $R^{12}$  has the same definition as  $R^7$  defined earlier, q is zero or an integer from 0-8, and T is defined either as (1) a nucleophilic center such as, but not limited, to a nitrogen, oxygen or sulfur-containing group, capable of undergoing a nucleophilic substitution reaction with the leaving group  $T'$  or (2) a leaving group capable undergoing a nucleophilic substitution reaction with a nucleophilic group  $T'$  (such as, but not limited, to a nitrogen, oxygen or sulfur-containing nucleophilic group).  $T'$  has the same definition as T. In the present case, for example, a nucleophilic substitution reaction occurs when the attacking reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with the electron pair, leaving as an anionic intermediate. For a detailed discussion of the mechanism of aliphatic nucleophilic substitutions and a review of specific aliphatic nucleophilic

substitution reactions see *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, 4<sup>th</sup> Addition*. Jerry March (Ed.), John Wiley & Sons, New York (1992) 293-500 and the references therein. Compounds of the formulae **IVa**, **IVb**, or **IVc** may, of course, be employed in the methods described herein (especially, in the treatment of nuclear hormone receptor-associated conditions) without undergoing further reaction of T or T'.

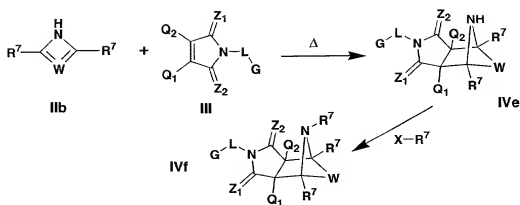
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## Scheme VIII



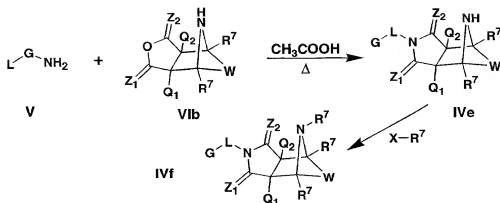
- An alternate approach to compounds of formula IVa, IVb and IVc is illustrated in Scheme VIII. For this approach, techniques such as those described in Schemes II, III and IV can be applied to the preparation of an intermediate of formula VIa, where T and q are as defined in Scheme VII. The intermediate of formula VIa can be reacted with a substituted amine of formula V, as described in Scheme II, to yield the compound of formula IVa, which is a compound of formula I where Y is O, A<sub>2</sub> is CR<sup>7</sup> and A<sub>1</sub> is C—(CH<sub>2</sub>)<sub>q</sub>—T. The compound of formula IVa can be treated in the manner described in Scheme VII to obtain compounds of formula IVb or IVc which are compounds of formula I where Y is O, A<sub>2</sub> is CR<sup>7</sup> and A<sub>1</sub> is C—(CH<sub>2</sub>)<sub>q</sub>—T'—R<sup>12</sup> or C—(CH<sub>2</sub>)<sub>q</sub>—T—R<sup>12</sup>, respectively.

## Scheme IX



- Scheme IX describes another approach to incorporating further substitution
- 5 onto a compound of formula I. As illustrated in Scheme IX (where X is a leaving group), a diene of formula IIb can be reacted with a dienophile of formula III, as described in Scheme I, to yield a compound of formula IVe, which is a compound of formula I where Y is NH, and  $A_1$  and  $A_2$  are  $CR^7$ . The compound of formula IVe can be functionalized at the free amine by reacting with a variety of electrophilic agents
- 10 such as acid halides or alkyl halides in the presence of base, for example by methods known by one skilled in the art and described in Scheme V, to yield a compound of formula IVf, which is a compound of formula I where Y is  $NR^7$  and  $A_1$  and  $A_2$  are  $CR^7$ .

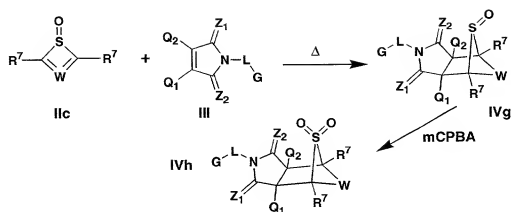
Scheme X



- 5 An alternate approach to compounds of formula **IVe** and **IVf** is illustrated in Scheme X. For this approach, techniques as described in Schemes **II**, **III** and **IV** can be applied to the preparation of an intermediate of formula **VIb**. The intermediate of formula **VIb** can be reacted with a substituted amine of formula **V**, as described in Scheme **II**, to yield a compound of formula **IVe**, which is a compound of
- 10 formula **I** where  $Y$  is  $NH$ , and  $A_1$  and  $A_2$  are  $CR^7$ . The latter intermediate can be treated in the manner described in Scheme **V** to obtain a compound of formula **IVf**, which is a compound of formula **I** where  $Y$  is  $NR^7$ , and  $A_1$  and  $A_2$  are  $CR^7$ .

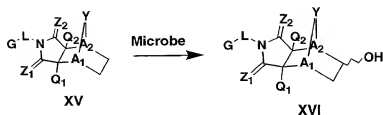


Scheme XI



- 5                Scheme **XI** describes another approach to incorporating additional substitution onto a compound of formula **I**. As illustrated in Scheme **XI**, a diene of formula **IIc** can be reacted with a dienophile of formula **III**, as described in Scheme **I**, to yield a compound of formula **IVg**, which is a compound of formula **I** where Y is SO and A<sub>1</sub> and A<sub>2</sub> are CR<sup>7</sup>. A compound of formula **IVg** can be treated with an
- 10                oxidizing agent such as mCPBA, as described in Scheme **VI**, to yield a compound of formula **IVh**, which is a compound of formula **I** where Y is SO<sub>2</sub> and A<sub>1</sub> and A<sub>2</sub> are CR<sup>7</sup>.

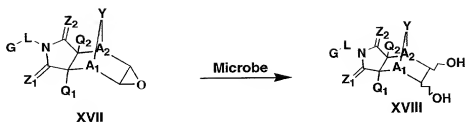
## Scheme XII



5

- Scheme **XII** describes another approach to incorporating additional substitution onto a compound of formula **I**. As illustrated in Scheme **XII**, a compound of formula **XV**, which can be prepared in accordance with the above Schemes, can be incubated in the presence of a suitable enzyme or microorganism resulting in the formation of a hydroxylated analog of formula **XVI**. Such a process can be employed to yield regiospecific as well as enantiospecific incorporation of a hydroxyl group into a molecule of formula **XV** by a specific microorganism or by a series of different microorganisms. Such microorganisms can, for example, be bacterial, yeast or fungal in nature and can be obtained from distributors such as ATCC or identified for use in this method such as by methods known to one skilled in the art. Compound **XVI** is a compound of formula **I** where Y is as described above and A<sub>1</sub> and A<sub>2</sub> are preferably CR<sup>7</sup>.

## Scheme XIII

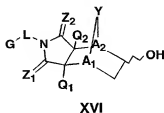


5

Scheme XIII describes another approach to incorporating additional substitution onto a compound of formula I. As illustrated in Scheme XIII, a compound of formula XVII, which can be prepared in accordance with the above Schemes, can be incubated in the presence of a suitable enzyme or microorganism resulting in the formation of a diol analog of formula XVIII. Such a process can be employed to yield regiospecific as well as enantiospecific transformation of a compound of formula XVII to a 1-2 diol of formula XVIII by a specific microorganism or by a series of different microorganisms. Such microorganisms can, for example, be bacterial, yeast or fungal in nature and can be obtained from distributors such as ATCC or identified for use in this method such as by methods known to one skilled in the art. Compound XVIII is a compound of formula I where Y is as described above and A<sub>1</sub> and A<sub>2</sub> are preferably CR<sup>7</sup>.

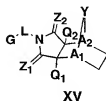
The present invention also provides the methods of Schemes XII and XIII.

Thus, in one embodiment, the present invention provides a method for preparation of a compound of the following formula XVI, or salt thereof:



where the symbols are as defined herein,

comprising the steps of contacting a compound of the following formula XV, or salt thereof:

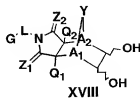


5

where the symbols are as defined above;  
with an enzyme or microorganism capable of catalyzing the hydroxylation of said compound XV to form said compound XVI, and effecting said hydroxylation.

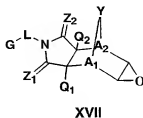
10

In another preferred embodiment, the present invention provides a method for preparation of a compound of the following formula XVIII, or salt thereof:



15

where the symbols are as defined herein,  
comprising the steps of contacting a compound of the following formula XVII, or salt thereof:



20

where the symbols are as defined above;  
with an enzyme or microorganism capable of catalyzing the opening of the epoxide ring of compound XVII to form the diol of said compound XVIII, and effecting said ring opening and diol formation.

25

All stereoconfigurations of the unspecified chiral centers of the compounds of the formulae XV, XVI, XVII and XVIII are contemplated in the methods of the present invention, either alone (that is, substantially free of other stereoisomers) or in admixture with other stereoisomeric forms. Conversion of one isomer selectively

(e.g., hydroxylation of the exo isomer preferentially to hydroxylation of the endo isomer) when contacting an isomeric mixture is a preferred embodiment of the invention. Conversion to one isomer selectively (e.g., hydroxylation on the exo face "exo isomer" preferentially to the endo face "endo isomer" or regioselective opening of an epoxide to form only one of two possible regioisomers of a trans diol) is a preferred embodiment of the invention. Hydroxylation of an achiral intermediate to form a single optical isomer of the hydroxylated product is also a preferred embodiment of the invention. Resolution of a racemic mixture of an intermediate by selective hydroxylation, or epoxide ring opening and diol formation, to generate one of the two possible optical isomers is also a preferred embodiment of the invention. The term "resolution" as used herein denotes partial, as well as, preferably, complete resolution.

The terms "enzymatic process" or "enzymatic method", as used herein, denote a process or method of the present invention employing an enzyme or microorganism. The term "hydroxylation", as used herein, denotes the addition of a hydroxyl group to a methylene group as described above. Hydroxylation can be achieved, for example, by contact with molecular oxygen according to the methods of the present invention. Diol formation can be achieved, for example, by contact with water according to the methods of the present invention. Use of "an enzyme or microorganism" in the present methods includes use of two or more, as well as a single, enzyme or microorganism.

The enzyme or microorganism employed in the present invention can be any enzyme or microorganism capable of catalyzing the enzymatic conversions described herein. The enzymatic or microbial materials, regardless of origin or purity, can be employed in the free state or immobilized on a support such as by physical adsorption or entrapment. Microorganisms or enzymes suitable for use in the present invention can be selected by screening for the desired activity, for example, by contacting a candidate microorganism or enzyme with a starting compound XV or XVII or salt thereof, and noting conversion to the corresponding compound XVI or XVIII or salt thereof. The enzyme may, for example, be in the form of animal or plant enzymes or mixtures thereof, cells of microorganisms, crushed cells, extracts of cells, or of synthetic origin.

Exemplary microorganisms include those within the genera: *Streptomyces* or *Amycolatopsis*. Particularly preferred microorganisms are those within the species *Streptomyces griseus*, especially *Streptomyces griseus* ATCC 10137, and *Amycolatopsis orientalis* such as ATCC 14930, ATCC 21425, ATCC 35165, ATCC 39444, ATCC 43333, ATCC 43490, ATCC 53550, ATCC 53630, and especially

ATCC 43491. The term "ATCC" as used herein refers to the accession number of the American Type Culture Collection, 10801 University Blvd., Manassas Virginia 20110-2209, the depository for the organism referred to. It should be understood that mutants of these organisms are also contemplated by the present invention, for use in the methods described herein, such as those modified by the use of chemical, physical (for example, X-rays) or biological means (for example, by molecular biology techniques).

Preferred enzymes include those derived from microorganisms, particularly those microorganisms described above. Enzymes may be isolated, for example, by extraction and purification methods such as by methods known to those of ordinary skill in the art. An enzyme may, for example, be used in its free state or in immobilized form. One embodiment of the invention is that where an enzyme is adsorbed onto a suitable carrier, e.g., diatomaceous earth (porous Celite Hyflo Supercel), microporous polypropylene (Enka Accurel® polypropylene powder), or a nonionic polymeric adsorbent such as Amberlite® XAD-2 (polystyrene) or XAD-7 (polyacrylate) from Rohm and Haas Co. When employed to immobilize an enzyme, a carrier may control the enzyme particle size and prevent aggregation of the enzyme particles when used in an organic solvent. Immobilization can be accomplished, for example, by precipitating an aqueous solution of the enzyme with cold acetone in the presence of the Celite Hyflo Supercel followed by vacuum drying, or in the case of a nonionic polymeric adsorbent, incubating enzyme solutions with adsorbent on a shaker, removing excess solution and drying enzyme-adsorbent resins under vacuum. While it is desirable to use the least amount of enzyme possible, the amount of enzyme required will vary depending upon the specific activity of the enzyme used.

Hydroxylation as described above can occur *in vivo*. For example, liver enzyme can selectively, relative to the endo isomer, hydroxylate the exo isomer of a compound of the present invention. In conducting the methods of the present invention outside the body, liver microsomal hydroxylase can be employed as the enzyme for catalysis.

These processes may also be carried out using microbial cells containing an enzyme having the ability to catalyze the conversions. When using a microorganism to perform the conversion, these procedures are conveniently carried out by adding the cells and the starting material to the desired reaction medium.

Where microorganisms are employed, the cells may be used in the form of intact wet cells or dried cells such as lyophilized, spray-dried or heat-dried cells, or in the form of treated cell material such as ruptured cells or cell extracts. Cell extracts immobilized on Celite® or Accurel® polypropylene as described earlier may also be

employed. The use of genetically engineered organisms is also contemplated. The host cell may be any cell, e.g. *Escherichia coli*, modified to contain a gene or genes for expressing one or more enzymes capable of catalysis as described herein.

- Where one or more microorganisms are employed, the enzymatic methods of the present invention may be carried out subsequent to the fermentation of the microorganism (two-stage fermentation and conversion), or concurrently therewith, that is, in the latter case, by *in situ* fermentation and conversion (single-stage fermentation and conversion).

- Growth of the microorganisms can be achieved by one of ordinary skill in the art by the use of an appropriate medium. Appropriate media for growing microorganisms include those which provide nutrients necessary for the growth of the microbial cells. A typical medium for growth includes necessary carbon sources, nitrogen sources, and elements (e.g. in trace amounts). Inducers may also be added. The term "inducer", as used herein, includes any compound enhancing formation of the desired enzymatic activity within the microbial cell.

- Carbon sources can include sugars such as maltose, lactose, glucose, fructose, glycerol, sorbitol, sucrose, starch, mannitol, propylene glycol, and the like; organic acids such as sodium acetate, sodium citrate, and the like; and alcohols such as ethanol, propanol and the like.

- Nitrogen sources can include N-Z amine A, corn steep liquor, soy bean meal, beef extracts, yeast extracts, molasses, baker's yeast, tryptone, nutrisoy, peptone, yeastamin, amino acids such as sodium glutamate and the like, sodium nitrate, ammonium sulfate and the like.

- Trace elements can include magnesium, manganese, calcium, cobalt, nickel, iron, sodium and potassium salts. Phosphates may also be added in trace or, preferably, greater than trace amounts.

The medium employed can include more than one carbon or nitrogen source or other nutrient.

- Preferred media for growth include aqueous media. The agitation and aeration of the reaction mixture affects the amount of oxygen available during the conversion process when conducted, for example, in shake-flask cultures or fermentor tanks during growth of microorganisms.

- Incubation of the reaction medium is preferably at a temperature between about 4 and about 60°C. The reaction time can be appropriately varied depending upon the amount of enzyme used and its specific activity. Reaction times may be reduced by increasing the reaction temperature and/or increasing the amount of enzyme added to the reaction solution.

It is also preferred to employ an aqueous liquid as the reaction medium, although an organic liquid, or a miscible or immiscible (biphasic) organic/aqueous liquid mixture, may also be employed. The amount of enzyme or microorganism employed relative to the starting material is selected to allow catalysis of the enzymatic conversions of the present invention.

Solvents for the organic phase of a biphasic solvent system may be any organic solvent immiscible in water, such as toluene, cyclohexane, xylene, trichlorotrifluoroethane and the like. The aqueous phase is conveniently of water, preferably deionized water, or a suitable aqueous buffer solution, especially a phosphate buffer solution. The biphasic solvent system preferably comprises between about 10 to 90 percent by volume of organic phase and between about 90 to 10 percent by volume of aqueous phase, and most preferably contains at or about 20 percent by volume of organic phase and at or about 80 percent by volume of the aqueous phase.

An exemplary embodiment of such processes starts with preparation of an aqueous solution of the enzyme(s) or microbes to be used. For example, the preferred enzyme(s) or microbes can be added to a suitable amount of an aqueous solvent, such as phosphate buffer or the like. This mixture is preferably adjusted to and maintained at a desired pH.

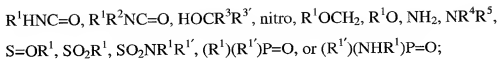
The compounds XVI and XVIII produced by the processes of the present invention can be isolated and purified, for example, by methods such as extraction, distillation, crystallization, and column chromatography.

### Preferred Compounds

A preferred subgenus of the compounds of the present invention includes compounds of the formula I or salts thereof wherein one or more, preferably all, of the following substituents are as defined below:

G is an aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN,  $R^1OC=O$ ,  $R^1C=O$ ,





$Z_1$  is O, S, NH, or  $NR^6$ ;

$Z_2$  is O, S, NH, or  $NR^6$ ;

5  $A_1$  is  $CR^7$  or N;

$A_2$  is  $CR^7$  or N;

Y is J-J'-J'' where J is  $(CR^7R^7)^n$  and  $n = 0-3$ , J' is a bond or O, S, S=O,  $SO_2$ , NH,

10  $OC=O$ ,  $C=O$ ,  $NR^7$ ,  $CR^7R^7$ ,  $R^2P=O$ ,  $R^2P=S$ ,  $R^2OP=O$ ,  $R^2NHP=O$ ,  $OP=OOR^2$ ,  
 $OP=ONHR^2$ ,  $OP=OR^2$ ,  $OSO_2$ ,  $NHNH$ ,  $NHNR^6$ ,  $NR^6NH$ ,  $N=N$ , cycloalkyl or  
substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo  
or substituted heterocyclo, and J'' is  $(CR^7R^7)^n$  and  $n = 0-3$ , where Y is not a  
bond;

W is  $CR^7R^7-CR^7R^7$ ,  $CR^7R^7-C=O$ ,  $NR^9-CR^7R^7$ ,  $N=CR^8$ ,  $N=N$ ,  $NR^9-NR^9$ ,  
cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl,  
15 heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein,  
when W is not  $NR^9-CR^7R^7$ ,  $N=CR^8$ ,  $N=N$ ,  $NR^9-NR^9$ , or heterocyclo or  
substituted heterocyclo, then J' must be O, S, S=O,  $SO_2$ , NH,  $NR^7$ ,  $OP=OOR^2$ ,  
 $OP=ONHR^2$ ,  $OSO_2$ ,  $NHNH$ ,  $NHNR^6$ ,  $NR^6NH$ , or  $N=N$ ;

$Q_1$  is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or  
20 substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl,  
heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted  
arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo  
(e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo,  
CN,  $R^1OC=O$ ,  $R^4C=O$ ,  $R^5R^6NC=O$ ,  $HOCR^7R^7$ , nitro,  $R^1OCH_2$ ,  $R^1O$ ,  $NH_2$ , or  
25  $NR^4R^5$ ;

$Q_2$  is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or  
substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl,  
heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted  
arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo  
30 (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo,

CN,  $R^1OC=O$ ,  $R^4C=O$ ,  $R^5R^6NC=O$ ,  $HO CR^7R^{7'}$ , nitro,  $R^1OCH_2$ ,  $R^1O$ ,  $NH_2$ , or  $NR^4R^5$ ;

L is a bond,  $(CR^7R^{7'})_n$ ,  $NH$ ,  $NR^5$  or  $NR^5(CR^7R^{7'})_n$ , where  $n = 0-3$ ;

- 5  $R^1$  and  $R^{1'}$  are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;
- 10  $R^2$  is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;
- 15  $R^3$  and  $R^{3'}$  are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,
- 20 halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino,  $NR^1R^2$ , thiol, alkylthio or substituted alkylthio;
- 25  $R^4$  is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  $R^1C=O$ ,  $R^1NHC=O$ , or
- 30  $SO_2NR^1R^{1'}$ ;

- $R^5$  is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  $R^1C=O$ ,  $R^1NHC=O$ ,  $SO_2R^1$ , or  $SO_2NR^1R^{1'}$ ;
- $R^6$  is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  $CN$ ,  $OH$ ,  $OR^1$ ,  $R^1C=O$ ,  $R^1NHC=O$ ,  $SO_2R^1$ , or  $SO_2NR^1R^{1'}$ ;
- $R^7$  and  $R^7$  are each independently  $H$ , alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo,  $CN$ ,  $OR^1$ , nitro, hydroxylamine, hydroxylamide, amino,  $NHR^4$ ,  $NR^2R^5$ ,  $NOR^1$ , thiol, alkylthio or substituted alkylthio,  $R^1C=O$ ,  $R^1(C=O)O$ ,  $R^1OC=O$ ,  $R^1NHC=O$ ,  $SOR^1$ ,  $PO_3R^1R^{1'}$ ,  $R^1R^{1'}NC=O$ ,  $C=OSR^1$ ,  $SO_2R^1$ , or  $SO_2NR^1R^{1'}$ ;
- $R^8$  and  $R^8$  are each independently  $H$ , alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo,  $CN$ ,  $OR^1$ , amino,  $NHR^4$ ,  $NR^2R^5$ ,  $NOR^1$ , alkylthio or substituted alkylthio,  $C=OSR^1$ ,  $R^1OC=O$ ,  $R^1C=O$ ,  $R^1NHC=O$ ,  $R^1R^{1'}NC=O$ ,  $S=OR^1$ ,  $SO_2R^1$ ,  $PO_3R^1R^{1'}$ , or  $SO_2NR^1R^{1'}$ ;

- $R^9$  and  $R^{9'}$  are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl; cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH,  $OR^1$ ,  $R^1C=O$ ,  $R^1OC=O$ ,  $R^1NHC=O$ , or  $SO_2NR^1R^{1'}$ ;
- especially where the groups W and Y of this preferred subgenus are also within the definitions of W' and Y' of formula Ia, with the provisos (1) to (14) of said formula Ia where appropriate to this subgenus, and most preferably where (i) when Y' is -O- and W' is  $CR^7R^{7'}-CR^7R^{7'}$ ,  $A_1$  and  $A_2$  are not simultaneously CH; and (ii) when L is a bond, G is not an unsubstituted phenyl group.

- Another, more preferred subgenus of the compounds of the invention includes compounds of the formula I or salts thereof wherein one or more, preferably all, of the following substituents are as defined below:

- G is an aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN,  $R^1C=O$ ,  $R^1HNC=O$ ,  $R^1R^2NC=O$ ,  $HOCH^3R^3$ , nitro,  $R^1OCH_2$ ,  $R^1O$ ,  $NH_2$ ,  $NR^4R^5$ ,  $SO_2R^1$ , or  $SO_2NR^1R^{1'}$ ;
- $Z_1$  is O;
- $Z_2$  is O;
- $A_1$  is  $CR^7$ ;
- $A_2$  is  $CR^7$ ;
- Y is  $J-J'-J''$  where J is  $(CR^7R^{7'})_n$  and  $n = 0-3$ , J' is a bond or O, S,  $S=O$ ,  $SO_2$ , NH,  $NH^+$ ,  $CR^7R^{7'}$ ,  $R^2P=O$ ,  $R^2P=S$ ,  $R^2OP=O$ ,  $R^2NHP=O$ ,  $OP=OOR^2$ ,  $OP=ONHR^2$ ,

OP=OR<sup>2</sup>, OSO<sub>2</sub>, NHNH, NHNH<sup>6</sup>, NR<sup>6</sup>NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J'' is (CR<sup>7</sup>R<sup>7'</sup>)<sub>n</sub> and n = 0-3, where Y is not a bond;

- 5 W is CR<sup>7</sup>R<sup>7'</sup>—CR<sup>7</sup>R<sup>7'</sup>, CR<sup>7</sup>R<sup>7'</sup>—C=O, NR<sup>9</sup>—CR<sup>7</sup>R<sup>7'</sup>, N=CR<sup>8</sup>, N=N, NR<sup>9</sup>—NR<sup>9'</sup>, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein, when W is not NR<sup>9</sup>—CR<sup>7</sup>R<sup>7'</sup>, N=CR<sup>8</sup>, N=N, NR<sup>9</sup>—NR<sup>9'</sup>, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO<sub>2</sub>, NH, NR<sup>7</sup>, OP=OOR<sup>2</sup>,  
10 OP=ONHR<sup>2</sup>, OSO<sub>2</sub>, NHNH, NHNH<sup>6</sup>, NR<sup>6</sup>NH, or N=N;

Q<sub>1</sub> is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo  
15 (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R<sup>4</sup>C=O, R<sup>5</sup>R<sup>6</sup>NC=O, HOCR<sup>7</sup>R<sup>7'</sup>, nitro, R<sup>1</sup>OCH<sub>2</sub>, R<sup>1</sup>O, NH<sub>2</sub>, or NR<sup>4</sup>R<sup>5</sup>;

Q<sub>2</sub> is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted  
20 arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R<sup>4</sup>C=O, R<sup>5</sup>R<sup>6</sup>NC=O, HOCR<sup>7</sup>R<sup>7'</sup>, nitro, R<sup>1</sup>OCH<sub>2</sub>, R<sup>1</sup>O, NH<sub>2</sub>, or NR<sup>4</sup>R<sup>5</sup>;

L is a bond;

- R<sup>1</sup> and R<sup>1'</sup> are each independently H, alkyl or substituted alkyl, alkenyl or substituted  
25 alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;  
30 R<sup>2</sup> is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted

cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

- 5      $R^3$  and  $R^{3'}$  are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, alkoxy or substituted alkoxy, amino,  $NR^1R^2$ , alkylthio or substituted alkylthio;
- 10      $R^4$  is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  $R^1C=O$ ,  $R^1NHC=O$ , or  $SO_2NR^1R^{1'}$ ;
- 15      $R^5$  is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  $R^1C=O$ ,  $R^1NHC=O$ ,  $SO_2R^1$ , or  $SO_2NR^1R^{1'}$ ;
- 20      $R^6$  is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  $R^1C=O$ ,  $R^1NHC=O$ ,  $SO_2R^1$ , or  $SO_2NR^1R^{1'}$ ;
- 25      $R^6$  is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl,
- 30     heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl,

arylalkyl or substituted arylalkyl, CN, OH, OR<sup>1</sup>, R<sup>1</sup>C=O, R<sup>1</sup>NHC=O, SO<sub>2</sub>R<sup>1</sup>,  
or SO<sub>2</sub>NR<sup>1</sup>R<sup>1'</sup>;

5 R<sup>7</sup> and R<sup>7'</sup> are each independently H, alkyl or substituted alkyl, alkenyl or substituted  
alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl,  
cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted  
heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl  
or substituted cycloalkenylalkyl, heterocycloalkyl or substituted  
heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  
halo, CN, OR<sup>1</sup>, nitro, amino, NHR<sup>4</sup>, NR<sup>2</sup>R<sup>5</sup>, alkylthio or substituted alkylthio,  
10 R<sup>1</sup>C=O, R<sup>1</sup>(C=O)O, R<sup>1</sup>NHC=O, SO<sub>2</sub>R<sup>1</sup>, R<sup>1</sup>R<sup>1'</sup>NC=O, or SO<sub>2</sub>NR<sup>1</sup>R<sup>1'</sup>;

R<sup>8</sup> and R<sup>8'</sup> are each independently H, alkyl or substituted alkyl, alkenyl or substituted  
alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl,  
cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted  
heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or  
15 substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl,  
aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR<sup>1</sup>,  
amino, NHR<sup>4</sup>, NR<sup>2</sup>R<sup>5</sup>, alkylthio or substituted alkylthio, R<sup>1</sup>C=O, R<sup>1</sup>NHC=O,  
R<sup>1</sup>R<sup>1'</sup>NC=O, SO<sub>2</sub>R<sup>1</sup>, or SO<sub>2</sub>NR<sup>1</sup>R<sup>1'</sup>; and

R<sup>9</sup> and R<sup>9'</sup> are each independently H, alkyl or substituted alkyl, alkenyl or substituted  
20 alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl,  
cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted  
heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl  
or substituted cycloalkenylalkyl, heterocycloalkyl or substituted  
heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl,  
25 CN, OH, OR<sup>1</sup>, R<sup>1</sup>C=O, R<sup>1</sup>NHC=O, or SO<sub>2</sub>NR<sup>1</sup>R<sup>1'</sup>;

especially where the groups W and Y of this preferred subgenus are also within the  
definitions of W' and Y' of formula Ia, with the provisos (1) to (14) of said  
formula Ia where appropriate to this subgenus, and most preferably where (i)  
when Y' is -O- and W' is CR<sup>7</sup>R<sup>7'</sup>—CR<sup>7</sup>R<sup>7'</sup>, A<sub>1</sub> and A<sub>2</sub> are not simultaneously  
30 CH; and (ii) when L is a bond, G is not an unsubstituted phenyl group.

A particularly preferred subgenus of the compounds of the invention includes compounds of the formula I or salts thereof wherein one or more, preferably all, of the substituents are as defined below:

- G is an aryl (especially, phenyl or naphthyl) or heterocyclo (especially those heterocyclo groups G of the compounds of the Examples herein) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with substituents as exemplified in any of the compounds of the Examples herein;
- 10 L is a bond,  $(CR^7R^7)n$  (where n is 1 and  $R^7$  and  $R^7$  are each independently H, alkyl or substituted alkyl), or  $-CH_2-NH-$ ;
- $A_1$  and  $A_2$  are each independently  $CR^7$  where  $R^7$  (i) is hydrogen, alkyl or substituted alkyl, arylalkyl or substituted arylalkyl, alkenyl or substituted alkenyl (for example, alkenyl substituted with aryl (especially, phenyl or naphthyl) or substituted aryl, or alkenyl substituted with heterocyclo or substituted heterocyclo), aryl or substituted aryl, heterocyclo or substituted heterocyclo, heterocycloalkyl or substituted heterocycloalkyl, where, for each, preferred substituents are one or more groups selected from  $V^1$
- 15 (especially  $A_1$  and  $A_2$  groups of the formula  $CR^7$  where  $R^7$  for each of  $A_1$  and/or  $A_2$  is independently selected from unsubstituted  $C_{1-4}$  alkyl, or  $C_{1-4}$  alkyl which alkyl is substituted by one or more groups  $V^1$ ), or (ii) forms, together with  $R^7$  of a group W (especially where W is  $CR^7R^7-CR^7R^7$ ), a heterocyclic ring;
- 20  $V^1$  is OH, CN, halo,  $-O$ -aryl,  $-O$ -substituted aryl,  $-O$ -heterocyclo (e.g.,  $-O$ -(optionally substituted pyridinyl) or  $-O$ -(optionally substituted pyrimidinyl)),  $-O$ -substituted heterocyclo,  $-O-CO$ -alkyl,  $-O-CO$ -substituted alkyl,  $-O$ -(alkylsilyl),  $-O$ -arylalkyl,  $-O$ -substituted arylalkyl,  $-O-CO$ -alkyl,  $-O-CO$ -substituted alkyl,  $-O-CO$ -arylalkyl, -
- 30  $O-CO$ -substituted arylalkyl,  $-O-CO$ -aryl,  $-O-CO$ -substituted aryl,  $-O-CO$ -heterocyclo,  $-O-CO$ -substituted heterocyclo,  $-S$ -(optionally



substituted aryl)-NH-CO-(optionally substituted alkyl), -SO-  
 (optionally substituted aryl)-NH-CO-(optionally substituted alkyl), -  
 SO<sub>2</sub>-(optionally substituted aryl)-NH-CO-(optionally substituted  
 alkyl), -NH-SO<sub>2</sub>-aryl, -NH-SO<sub>2</sub>-substituted aryl, -NH-CO-O-  
 5 (optionally substituted arylalkyl), -NH-CO-O-alkyl, -NH-CO-O-  
 substituted alkyl, -NH-CO-alkyl, -NH-CO-substituted alkyl, -NH-  
 CO-aryl, -NH-CO-substituted aryl, -NH-CO-(optionally substituted  
 arylalkyl), -NH-CO-(optionally substituted alkyl)-O-(optionally  
 substituted aryl), -N(optionally substituted alkyl)(optionally  
 10 substituted aryl), -N(optionally substituted alkyl)(optionally  
 substituted arylalkyl), -COH, -COOH, -CO-O-alkyl, -CO-O-  
 substituted alkyl, -CO-O-optionally substituted arylalkyl, -CO-aryl,  
 -CO-substituted aryl, -O-CO-NH-aryl, -O-CO-NH-substituted aryl, -  
 CO-NH-aryl, -CO-NH-substituted aryl, -CO-NH-arylalkyl, -CO-NH-  
 15 substituted arylalkyl, -O-(optionally substituted aryl)-NH-CO-  
 (optionally substituted alkyl);

Y is -O-, -SO-, -N(V<sup>3</sup>)-, -CH<sub>2</sub>-N(V<sup>3</sup>)-, -CO-N(alkyl)-, -CH<sub>2</sub>-S-, -CH<sub>2</sub>-SO<sub>2</sub>;

V<sup>2</sup> is hydrogen, alkyl, arylalkyl, -CO-alkyl, -CO-O-aryl, -CO-O-arylalkyl;

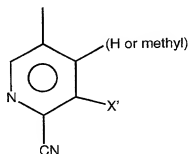
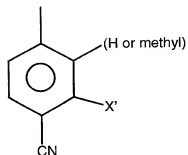
W is CR<sup>7</sup>R<sup>7'</sup>—CR<sup>8</sup>R<sup>8'</sup> (where R<sup>7</sup> and R<sup>7'</sup> are each independently selected  
 20 from H, OH, alkyl or substituted alkyl (such as hydroxyalkyl), or  
 where R<sup>7</sup> forms a heterocyclic ring together with R<sup>7</sup> of A<sub>1</sub> or A<sub>2</sub>,  
 CR<sup>8</sup>=CR<sup>8'</sup> (where R<sup>8</sup> and R<sup>8'</sup> are each independently selected from H,  
 alkyl or substituted alkyl (such as hydroxyalkyl)), CR<sup>7</sup>R<sup>7'</sup>—C=O  
 (where R<sup>7</sup> and R<sup>7'</sup> are each hydrogen, or where R<sup>7</sup> forms a  
 25 heterocyclic ring together with R<sup>7</sup> of A<sub>1</sub> or A<sub>2</sub>), N=CR<sup>8</sup> (where R<sup>8</sup> is  
 alkyl), cycloalkyl or substituted cycloalkyl, or heterocyclo or  
 substituted heterocyclo;

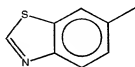
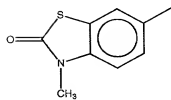
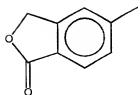
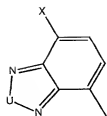
Z<sub>1</sub> and Z<sub>2</sub> are O; and

Q<sub>1</sub> and Q<sub>2</sub> are H.

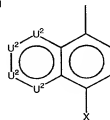
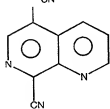
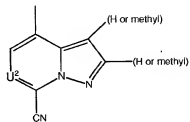
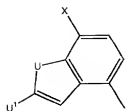
30 Preferred G-L groups are optionally substituted phenyl, optionally  
 substituted naphthyl and optionally substituted fused bicyclic heterocyclic

- groups such as optionally substituted benzo-fused heterocyclic groups (e.g., bonded to the remainder of the molecule through the benzene portion), especially such groups wherein the heterocyclic ring bonded to benzene has 5 members exemplified by benzoxazole, benzothiazole, benzothiadiazole, benzoxadiazole or benzothiophene, for example:

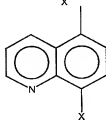




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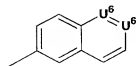


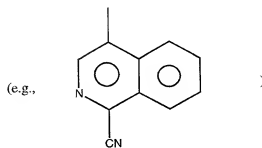
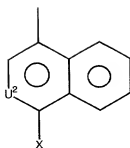
(e.g.,



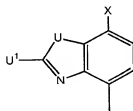
where X is OH or CN)

OR

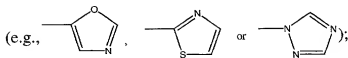
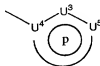




or



where

X = halo (especially F), OH, CN, NO<sub>2</sub> or

- 5 X' = halo (especially Cl, F, or I), CH<sub>3</sub>, CF<sub>3</sub>, CN or OCH<sub>3</sub>;

U is O or S (where S can optionally be oxygenated, e.g., to SO);

U<sup>1</sup> is CH<sub>3</sub> or CF<sub>3</sub>;

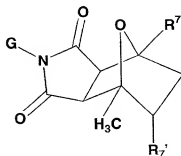
each U<sup>2</sup> is independently N, CH or CF;

U<sup>3</sup> is N, O or S;

- 10 U<sup>4</sup> and U<sup>5</sup>, together with the atoms to which they are bonded, form an optionally substituted 5-membered heterocyclic ring which can be partially unsaturated or aromatic and which contains 1 to 3 ring heteroatoms;
- each U<sup>6</sup> is independently CH or N; and

(p) denotes optional double bond(s) within the ring formed by U<sup>3</sup>, U<sup>4</sup> and U<sup>5</sup>.

An especially preferred subgenus includes compounds of the formula I having the following structure, or salts thereof:



where G is an optionally substituted phenyl, naphthyl or benzo-fused bicyclic heterocyclic group, R<sup>7</sup> is CH<sub>3</sub> or C<sub>1-4</sub>alkyl substituted by V<sup>1</sup>, and one R<sup>7</sup> is H or hydroxyl and the other is H.

Compounds where R<sup>7</sup> is hydroxyl can provide enhanced water solubility and metabolic stability, relative to the corresponding compounds where R<sup>7</sup> is H, in addition to having good permeability and high systemic blood levels. These hydroxyl-bearing compounds can be obtained *in vivo* by metabolism of the corresponding compound where R<sup>7</sup> is H, as well as by synthetic preparative methods such as those described herein.

### Use and Utility

The compounds of the present invention modulate the function of nuclear hormone receptors (NHR), and include compounds which are, for example, agonists, partial agonists, antagonists or partial antagonists of the androgen receptor (AR), the estrogen receptor (ER), the progesterone receptor (PR), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), the steroid and xenobiotic receptor (SXR), other steroid binding NHR's, the Orphan receptors or other NHR's. Selective modulation of one such NHR relative to others within the NHR family is preferred.

"Modulation" includes, for example, activation (e.g., agonist activity such as selective androgen receptor agonist activity) or inhibition (e.g., antagonist activity).

The present compounds are thus useful in the treatment of NHR-associated conditions. A "NHR-associated condition", as used herein, denotes a condition or disorder which can be treated by modulating the function of a NHR in a subject, wherein treatment comprises prevention (e.g., prophylactic treatment), partial alleviation or cure of the condition or disorder. Modulation may occur locally, for example, within certain tissues of the subject, or more extensively throughout a subject being treated for such a condition disorder.

The compounds of the present invention are useful for the treatment of a variety of conditions and disorders including, but not limited to, those described following:

Compounds of formula I can be applied as agonists, partial agonists, antagonists, or partial antagonists of the estrogen receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the estrogen receptor pathway. Applications of said compounds include but are not limited to: osteoporosis, hot flushes, vaginal dryness, prostate cancer, breast cancer, endometrial cancer, cancers expressing the estrogen receptor such as the aforementioned cancers and others, contraception, pregnancy termination, menopause, amenorrhea, and dysmenorrhea.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the progesterone receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the progesterone receptor pathway. Applications of said compounds include but are not limited to: breast cancer, other cancers containing the progesterone receptor, endometriosis, cachexia, contraception, menopause, cyclesynchrony, meningioma, dysmenorrhea, fibroids, pregnancy termination, labor induction and osteoporosis.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the glucocorticoid receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the glucocorticoid receptor pathway. Applications of said compounds include but are not limited to: inflammatory diseases, autoimmune diseases, prostate cancer, breast

cancer, Alzheimer's disease, psychotic disorders, drug dependence, non-insulin dependent Diabetes Mellitus, and as dopamine receptor blocking agents or otherwise as agents for the treatment of dopamine receptor mediated disorders.

- Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the mineralocorticoid receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the mineralocorticoid receptor pathway. Applications of said compounds include but are not limited to: drug withdrawal syndrome and inflammatory diseases.
- Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the aldosterone receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the aldosterone receptor pathway. One application of said compounds includes but is not limited to: congestive heart failure.
- Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the androgen receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the androgen receptor pathway. Applications of said compounds include but are not limited to: hirsutism, acne, seborrhea, Alzheimer's disease, androgenic alopecia, hypogonadism, hyperpilosity, benign prostate hypertrophy, adenomas and neoplasies of the prostate (such as advanced metastatic prostate cancer), treatment of benign or malignant tumor cells containing the androgen receptor such as is the case for breast, brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers, pancreatic cancers modulation of VCAM expression and applications therein for the treatment of heart disease, inflammation and immune modulations, modulation of VEGF expression and the applications therein for use as antiangiogenic agents, osteoporosis, suppressing spermatogenesis, libido, cachexia, endometriosis, polycystic ovary syndrome, anorexia, androgen supplement for age related decreased testosterone levels in men, male menopause, male hormone replacement, male and female sexual dysfunction, and inhibition of muscular atrophy in ambulatory patients. For example, pan AR modulation is contemplated, with prostate selective AR modulation ("SARM") being particularly preferred, such as for the treatment of early stage prostate cancers. .



Compounds of formula I can be applied as (preferably, selective) antagonists of the mutated androgen receptor, for example, found in many tumor lines. Examples of such mutants are those found in representative prostate tumor cell lines such as LNCap, (T877A mutation, Biophys. Acta, 187, 1052 (1990)), PCa2b, (L701H & T877A mutations, J. Urol., 162, 2192 (1999)) and CWR22, (H874Y mutation, Mol. Endo., 11, 450 (1997)). Applications of said compounds include but are not limited to: adenomas and neoplasies of the prostate, breast cancer and endometrial cancer.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the steroid and xenobiotic receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the steroid and xenobiotic receptor pathway. Applications of said compounds include but are not limited to: treatment of dysregulation of cholesterol homeostasis, attenuation of metabolism of pharmaceutical agents by co-administration of an agent (compound of the present invention) which modulates the P450 regulator effects of SXR.

Along with the aforementioned NHR, there also exist a number of NHR for which the activating or deactivating ligands may not be characterized. These proteins are classified as NHR due to strong sequence homology to other NHR, and are known as the Orphan receptors. Because the Orphan receptors demonstrate strong sequence homology to other NHR, compounds of formula I include those which serve as modulators of the function of the Orphan NHR. Orphan receptors which are modulated by NHR modulators such as compounds within the scope of formula I are exemplified, but not limited to, those listed in Table 1. Exemplary therapeutic applications of modulators of said Orphan receptors are also listed in Table 1, but are not limited to the examples therein.

**Table 1.** Exemplary Orphan nuclear hormone receptors, form (M = monomeric, D = heterodimeric, H = homodimeric), tissue expression and target therapeutic applications. (CNS=central nervous system)

<u>Receptor</u>	<u>Form</u>	<u>Tissue Expression</u>	<u>Target Therapeutic Application</u>
NURR1	M/D	Dopaminergic Neurons	Parkinson's Disease

	RZR $\beta$	M	Brain (Pituitary), Muscle	Sleep Disorders
	ROR $\alpha$	M	Cerebellum, Purkinje Cells	Arthritis, Cerebellar Ataxia
	NOR-1	M	Brain, Muscle, Heart, Adrenal, Thymus	CNS Disorders, Cancer
5	NGFI-B $\beta$	M/D	Brain	CNS Disorders
	COUP-Tf $\alpha$	H	Brain	CNS Disorders
	COUP-Tf $\beta$	H	Brain	CNS Disorders
	COUP-Tf $\gamma\chi$	H	Brain	CNS Disorders
	Nur77	H	Brain, Thymus, Adrenals	CNS Disorders
10	Rev-ErbA $\alpha$	H	Muscle, Brain (Ubiquitous)	Obesity
	HNF4 $\alpha$	H	Liver, Kidney, Intestine	Diabetes
	SF-1	M	Gonads, Pituitary	Metabolic Disorders
	LXR $\alpha,\beta$	D	Kidney (Ubiquitous)	Metabolic Disorders
	GCNF	M/H	Testes, Ovary	Infertility
15	ERR $\alpha,\beta$	M	Placenta, Bone	Infertility, Osteoporosis
	FXR	D	Liver, Kidney	Metabolic Disorders
	CAR $\alpha$	H	Liver, Kidney	Metabolic Disorders
	PXR	H	Liver, Intestine	Metabolic Disorders
	COUP-TF2 (ARP1)	D	Testis	Oncology/angiogenesis
20				
	RORbeta	M	CNS, retina, pineal gland	Metabolic Disorders

- The present invention thus provides methods for the treatment of NHR-associated conditions, comprising the step of administering to a subject in need thereof at least one compound of formula I in an amount effective therefor. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods (for example, separately, or formulated together as a fixed dose). In the methods of the present invention, such other therapeutic agent(s) can be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula I capable of treating a NHR-associated

condition in an amount effective therefor, and a pharmaceutically acceptable carrier (vehicle or diluent). The compositions of the present invention can contain other therapeutic agents as described below, and can be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical  
5 additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

It should be noted that the compounds of the present invention are, without limitation as to their mechanism of action, useful in treating any of the conditions or  
10 disorders listed or described herein such as inflammatory diseases or cancers, or other proliferate diseases, and in compositions for treating such conditions or disorders. Such conditions and disorders include, without limitation, any of those described previously, as well as those described following such as: maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or  
15 age-related functional decline ("ARFD") in the elderly (e.g., sarcopenia); treatment of catabolic side effects of glucocorticoids; prevention and/or treatment of reduced bone mass, density or growth (e.g., osteoporosis and osteopenia); treatment of chronic fatigue syndrome (CFS); chronic malalgia; treatment of acute fatigue syndrome and muscle loss following elective surgery  
20 (e.g., post-surgical rehabilitation); acceleration of wound healing; accelerating bone fracture repair (such as accelerating the recovery of hip fracture patients); accelerating healing of complicated fractures, e.g. distraction osteogenesis; in joint replacement; prevention of post-surgical adhesion formation; acceleration of tooth repair or growth; maintenance of sensory function (e.g., hearing, sight,  
25 olfaction and taste); treatment of periodontal disease; treatment of wasting secondary to fractures and wasting in connection with chronic obstructive pulmonary disease (COPD), chronic liver disease, AIDS, weightlessness, cancer cachexia, burn and trauma recovery, chronic catabolic state (e.g., coma),

- eating disorders (e.g., anorexia) and chemotherapy; treatment of  
 cardiomyopathy; treatment of thrombocytopenia; treatment of growth  
 retardation in connection with Crohn's disease; treatment of short bowel  
 syndrome; treatment of irritable bowel syndrome; treatment of inflammatory  
 5 bowel disease; treatment of Crohn's disease and ulcerative colitis; treatment of  
 complications associated with transplantation; treatment of physiological short  
 stature including growth hormone deficient children and short stature  
 associated with chronic illness; treatment of obesity and growth retardation  
 associated with obesity; treatment of anorexia (e.g., associated with cachexia or  
 10 aging); treatment of hypercortisolism and Cushing's syndrome; Paget's disease;  
 treatment of osteoarthritis; induction of pulsatile growth hormone release;  
 treatment of osteochondrodysplasias; treatment of depression, nervousness,  
 irritability and stress; treatment of reduced mental energy and low self-esteem  
 (e.g., motivation/assertiveness); improvement of cognitive function (e.g., the  
 15 treatment of dementia, including Alzheimer's disease and short term memory  
 loss); treatment of catabolism in connection with pulmonary dysfunction and  
 ventilator dependency; treatment of cardiac dysfunction (e.g., associated with  
 valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart  
 failure); lowering blood pressure; protection against ventricular dysfunction or  
 20 prevention of reperfusion events; treatment of adults in chronic dialysis;  
 reversal or slowing of the catabolic state of aging; attenuation or reversal of  
 protein catabolic responses following trauma (e.g., reversal of the catabolic  
 state associated with surgery, congestive heart failure, cardiac myopathy, burns,  
 cancer, COPD etc.); reducing cachexia and protein loss due to chronic illness  
 25 such as cancer or AIDS; treatment of hyperinsulinemia including  
 nesidioblastosis; treatment of immunosuppressed patients; treatment of wasting  
 in connection with multiple sclerosis or other neurodegenerative disorders;  
 promotion of myelin repair; maintenance of skin thickness; treatment of

- metabolic homeostasis and renal homeostasis (e.g., in the frail elderly); stimulation of osteoblasts, bone remodeling and cartilage growth; regulation of food intake; treatment of insulin resistance, including NIDDM, in mammals (e.g., humans); treatment of insulin resistance in the heart; improvement of
- 5 sleep quality and correction of the relative hypsomatotropism of senescence due to high increase in REM sleep and a decrease in REM latency; treatment of hypothermia; treatment of congestive heart failure; treatment of lipodystrophy (e.g., in patients taking HIV or AIDS therapies such as protease inhibitors); treatment of muscular atrophy (e.g., due to physical inactivity, bed rest or
- 10 reduced weight-bearing conditions); treatment of musculoskeletal impairment (e.g., in the elderly); improvement of the overall pulmonary function; treatment of sleep disorders; and the treatment of the catabolic state of prolonged critical illness; treatment of hirsutism, acne, seborrhea, androgenic alopecia, anemia, hyperpilosity, benign prostate hypertrophy, adenomas and neoplasies of the
- 15 prostate (e.g., advanced metastatic prostate cancer) and malignant tumor cells containing the androgen receptor, such as is the case for breast, brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers; cancers of the skin, pancreas, endometrium, lung and colon; osteosarcoma; hypercalcemia of malignancy; metastatic bone disease; treatment of spermatogenesis,
- 20 endometriosis and polycystic ovary syndrome; counteracting preeclampsia, eclampsia of pregnancy and preterm labor; treatment of premenstrual syndrome; treatment of vaginal dryness; age related decreased testosterone levels in men, male menopause, hypogonadism, male hormone replacement, male and female sexual dysfunction (e.g., erectile dysfunction, decreased sex
- 25 drive, sexual well-being, decreased libido), male and female contraception, hair loss, Reaven's Syndrome and the enhancement of bone and muscle performance/strength; and the conditions, diseases, and maladies collectively

referenced to as "Syndrome X" or Metabolic Syndrome as detailed in  
Johannsson J. *Clin. Endocrinol. Metab.*, 82, 727-34 (1997).

5 The present compounds have therapeutic utility in the modulation of immune  
cell activation/proliferation, e.g., as competitive inhibitors of intercellular  
ligand/receptor binding reactions involving CAMs (Cellular Adhesion Molecules) and  
Leukointegrins. For example, the present compounds modulate LFA-ICAM 1, and  
are particularly useful as LFA-ICAM 1 antagonists, and in the treatment of all  
conditions associated with LFA-ICAM 1 such as immunological disorders. Preferred  
10 utilities for the present compounds include, but are not limited to: inflammatory  
conditions such as those resulting from a response of the non-specific immune system  
in a mammal (e.g., adult respiratory distress syndrome, shock, oxygen toxicity,  
multiple organ injury syndrome secondary to septicemia, multiple organ injury  
syndrome secondary to trauma, reperfusion injury of tissue due to cardiopulmonary  
15 bypass, myocardial infarction or use with thrombolysis agents, acute  
glomerulonephritis, vasculitis, reactive arthritis, dermatosis with acute inflammatory  
components, stroke, thermal injury, hemodialysis, leukapheresis, ulcerative colitis,  
necrotizing enterocolitis and granulocyte transfusion associated syndrome) and  
conditions resulting from a response of the specific immune system in a mammal  
20 (e.g., psoriasis, organ/tissue transplant rejection, graft vs. host reactions and  
autoimmune diseases including Raynaud's syndrome, autoimmune thyroiditis,  
dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes  
mellitus, uveitis, inflammatory bowel disease including Crohn's disease and ulcerative  
colitis, and systemic lupus erythematosus). The present compounds can be used in  
25 treating asthma or as an adjunct to minimize toxicity with cytokine therapy in the  
treatment of cancers. The present compounds can be employed in the treatment of all  
diseases currently treatable through steroid therapy. The present compounds may be  
employed for the treatment of these and other disorders alone or with other  
immunosuppressive or antiinflammatory agents. In accordance with the invention, a  
30 compound of the formula I can be administered prior to the onset of inflammation (so  
as to suppress an anticipated inflammation) or after the initiation of inflammation.

When provided prophylactically, the immunosuppressive compound(s) are preferably provided in advance of any inflammatory response or symptom (for example, prior to, at, or shortly after the time of an organ or tissue transplant but in advance of any symptoms or organ rejection). The prophylactic administration of a compound of the formula I prevents or attenuates any subsequent inflammatory response (such as, for example, rejection of a transplanted organ or tissue, etc.) Administration of a compound of the formula I attenuates any actual inflammation (such as, for example, the rejection of a transplanted organ or tissue).

The compounds of the formula I can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula I can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include

those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal  
5 adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

10 Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable  
15 solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

20 Exemplary compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier  
25 such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound of the present invention can be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 1 to 100 (for example, 15 or lower, especially 1 to 3 or less) mg/kg of body weight of active compound per day, which can be administered  
30 in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors



including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment  
5 include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to NHR-associated conditions.

As mentioned above, the compounds of the present invention can be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of NHR-associated conditions, e.g., an antibiotic or other  
10 pharmaceutically active material.

For example, the compounds of the present invention can be combined with growth promoting agents, such as, but not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No.  
15 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

The compounds of the invention can also be used in combination with growth hormone secretagogues such as GHRP-6, GHRP-1 (as described in U.S. Patent No. 4,411,890 and publications WO 89/07110 and WO 89/07111), GHRP-2 (as described in WO 93/04081), NN703 (Novo Nordisk), LY444711 (Lilly), MK-677  
20 (Merck), CP424391 (Pfizer) and B-HT920, or with growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2, or with alpha-adrenergic agonists, such as clonidine or serotonin 5-HT<sub>D</sub> agonists, such as sumatriptan, or agents which inhibit somatostatin or its release, such as phsyostigmine and pyridostigmine. A still further use of the disclosed compounds  
25 of the invention is in combination with parathyroid hormone, PTH(1-34) or bisphosphonates, such as MK-217 (alendronate).

A still further use of the compounds of the invention is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or other androgen receptor modulators, such as those disclosed in

Edwards, J. P. et al., *Bio. Med. Chem. Let.*, 9, 1003-1008 (1999) and Hamann, L. G. et al., *J. Med. Chem.*, 42, 210-212 (1999).

A further use of the compounds of this invention is in combination with progesterone receptor agonists ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA).

The compounds of the present invention can be employed alone or in combination with each other and/or other modulators of nuclear hormone receptors or other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents; anti-osteoporosis agents; anti-obesity agents; anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; anti-platelet agents; anti-thrombotic and thrombolytic agents; cardiac glycosides; cholesterol/lipid lowering agents; mineralocorticoid receptor antagonists; phosphodiesterase inhibitors; protein tyrosine kinase inhibitors; thyroid mimetics (including thyroid receptor agonists); anabolic agents; HIV or AIDS therapies; therapies useful in the treatment of Alzheimer's disease and other cognitive disorders; therapies useful in the treatment of sleeping disorders; anti-proliferative agents; and anti-tumor agents.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g., metformin), glucosidase inhibitors (e.g., acarbose), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH fragment, raloxifene, calcitonin, steroidal or non-steroidal progesterone receptor agonists, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM), estrogen and AP-1 inhibitors.

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors, such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), a serotonin (and dopamine) reuptake inhibitor, such as sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), a thyroid receptor beta drug, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), and/or an anorectic agent, such as dexamphetamine, phentermine, phenylpropanolamine or mazindol.

Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel®, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen®, Celebrex®, Vioxx®), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®) integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK)

inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome (e.g., Zelmac® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

Example of suitable anti-anxiety agents for use in combination with the  
5 compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and hydroxyzine pamoate.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

10 Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide,  
15 polythiazide, benzthiazide, ethacrynic acid, tricyclic, chlorthalidone, furosemide, musolimine, bumetanide, triamterene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrisentan  
20 and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

Examples of suitable anti-platelet agents for use in combination with the  
25 compounds of the present invention include GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, tirofiban), P2Y<sub>12</sub> antagonists (e.g., clopidogrel, ticlopidine, CS-747), thromboxane receptor antagonists (e.g., ifetroban), aspirin, and PDE-III inhibitors (e.g., dipyridamole) with or without aspirin.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)), squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, cholesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include spironolactone and eplerenone.

Examples of suitable phosphodiesterase inhibitors for use in combination with the compounds of the present invention include PDEIII inhibitors such as cilostazol, and PDE V inhibitors such as sildenafil.

Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone, TRH diethylstilbesterol, estrogens,  $\beta$ -agonists, theophylline, anabolic steroids, dehydroepiandrosterone, enkephalins, E-series prostagladins, retinoic acid and compounds as disclosed in U.S. Pat. No. 3,239,345, e.g., Zeranol®; U.S. Patent No. 4,036,979, e.g., Sulbenox® or peptides as disclosed in U.S. Pat. No. 4,411,890.

Examples of suitable HIV or AIDS therapies for use in combination with the compounds of the present invention include indinavir sulfate, saquinavir, saquinavir mesylate, zalcitabine, didanosine, stavudine, and megestrol acetate.

Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present invention include donepezil, tacrine, revastigmine, 5HT<sub>6</sub>, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs

5 blockers.

Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present invention include melatonin analogs, melatonin receptor antagonists, ML1B agonists, and GABA/NMDA receptor antagonists.

10 Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, paclitaxel, FK 506, and adriamycin.

Examples of suitable anti-tumor agents for use in combination with the compounds of the present invention include paclitaxel, adriamycin, epothilones, 15 cisplatin and carboplatin.

Compounds of the present invention can further be used in combination with nutritional supplements such as those described in U.S. 5,179,080, especially in combination with whey protein or casin, amino acids (such as leucine, branched 20 amino acids and hydroxymethylbutyrate), triglycerides, vitamins (e.g., A, B<sub>6</sub>, B<sub>12</sub>, folate, C, D and E), minerals (e.g., selenium, magnesium, zinc, chromium, calcium and potassium), carnitine, lipoic acid, creatine, and coenzyme Q-10.

In addition, compounds of the present invention can be used in combination with therapeutic agents used in the treatment of sexual dysfunction, including but not 25 limited to PDE5 inhibitors, such as sildenafil or IC-351; with an antiresorptive agent, hormone replacement therapies, vitamin D analogues, calcitonins, elemental calcium and calcium supplements, cathepsin K inhibitors, MMP inhibitors, vitronectin receptor antagonists, Src SH<sub>2</sub> antagonists, vacular -H<sup>+</sup>-ATPase inhibitors, progesterone receptor agonists, ipriflavone, fluoride, RANK antagonists, PTH and its 30 analogues and fragments, Tibolone, HMG-CoA reductase inhibitors, SERM's, p38

inhibitors, prostanoids, 17-beta hydroxysteroid dehydrogenase inhibitors and Src kinase inhibitors.

Compounds of the present invention can be used in combination with male contraceptives, such as nonoxynol 9 or therapeutic agents for the treatment of hair loss, such as minoxidil and finasteride or chemotherapeutic agents, such as with LHRH agonists.

For their preferred anticancer or antiangiogenic use, the compounds of the present invention can be administered either alone or in combination with other anti-cancer and cytotoxic agents and treatments useful in the treatment of cancer or other proliferative diseases, for example, where the second drug has the same or different mechanism of action than the present compounds of formula I. Examples of classes of anti-cancer and cytotoxic agents useful in combination with the present compounds include but are not limited to: alkylating agents such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; EGFR inhibitors such as small molecule EGFR inhibitors, EGFR antibodies such as C225 (Erbix); antimetabolites such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes such as L-asparaginase; farnesyl-protein transferase inhibitors; 5 $\alpha$  reductase inhibitors; inhibitors of 17 $\beta$ -hydroxy steroid dehydrogenase type 3 or type 1; hormonal agents such as glucocorticoids, estrogens/ antiestrogens, androgens/ antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as taxanes, for example, paclitaxel (Taxol®), docetaxel (Taxotere®), and their analogs, and epothilones, such as epothilones A-F and their analogs; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators and monoclonal

antibodies. The compounds of the invention may also be used in conjunction with radiation therapy.

Representative examples of these classes of anti-cancer and cytotoxic agents include but are not limited to mechlorethamine hydrochloride, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustin, lomustine, semustine, streptozocin, thiotepa, dacarbazine, methotrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, etoposide, etoposide phosphate, teniposide, paclitaxel, tamoxifen, estramustine, estramustine phosphate sodium, flutamide, buserelin, leuprolide, pteridines, diynes, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethosone, gemcitabine hydrochloride, altretamine, and topotecan and any analogs or derivatives thereof.

Preferred member of these classes include, but are not limited to, paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, or porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosine, vindesine and leurosine.

Examples of anticancer and other cytotoxic agents include the following: epothonone derivatives as found in German Patent No. 4138042.8; WO 97/19086, WO 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO 99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 99/28324, WO 99/43653, WO 99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO 99/67252, WO 99/67253 and WO 00/00485; cyclin dependent kinase inhibitors as found in WO 99/24416 (see also U.S. Patent No. 6,040,321); and prenyl-protein transferase inhibitors as found in WO 97/30992 and WO 98/54966; and agents such as those described generically and specifically in U.S. Patent No. 6,011,029 (the compounds of which U.S. Patent can be employed together with any NHR modulators (including, but not limited to, those of present invention) such as AR modulators, ER



modulators, with LHRH modulators, or with surgical castration, especially in the treatment of cancer).

The combinations of the present invention can also be formulated or co-administered with other therapeutic agents that are selected for their particular  
5 usefulness in administering therapies associated with the aforementioned conditions. For example, the compounds of the invention may be formulated with agents to prevent nausea, hypersensitivity and gastric irritation, such as antiemetics, and H<sub>1</sub> and H<sub>2</sub> antihistaminics.

As it pertains to the treatment of cancer, the compounds of this invention are  
10 most preferably used alone or in combination with anti-cancer treatments such as radiation therapy and/or with cytostatic and/or cytotoxic agents, such as, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; inhibitors of farnesyl protein transferase, such as those described in U.S. Patent No. 6,011,029; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors, such as  
15 CPT-11 or topotecan; tubulin stabilizing agents, such as paclitaxel, docetaxel, other taxanes, or epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; antimetabolites, such as methotrexate; antiangiogenic agents, such as angiostatin, ZD6474, ZD6126 and comberstatin A2; kinase inhibitors, such as her2 specific antibodies, Iressa and CDK inhibitors; histone  
20 deacetylase inhibitors, such as CI-994 and MS-27-275. Such compounds may also be combined with agents which suppress the production of circulating testosterone such as LHRH agonists or antagonists or with surgical castration. Exemplary combination therapies (e.g., for the treatment of prostate cancer) for use with a compound of the present invention include an LHRH modulator or prednisone.

25 The present invention also contemplates kits, for example, for the treatment of prostate cancer, comprising a first container (such as a vial) containing a pharmaceutical formulation comprising a compound of the present invention, said compound optionally in a pharmaceutically acceptable carrier, and a second container (such as a vial) containing a pharmaceutical formulation comprising one or more  
30 agents (such as an LHRH modulator) to be used in combination with said compound of the present invention, said agent(s) optionally in a pharmaceutically acceptable carrier.

For example, known therapies for advanced metastatic prostate cancer include "complete androgen ablation therapy" wherein tumor growth is inhibited by controlling the supply of androgen to the prostate tissues via chemical castration (castration serves to inhibit the production of circulating testosterone (T) and dihydrotestosterone (DHT)) followed by the administration of androgen receptor (AR) antagonists (which inhibit the function T/DHT derived from the conversion of circulating androgen precursors to T/DHT by the prostate tissue). The compounds of the present invention can be employed as AR antagonists in complete ablation therapy, alone or in combination with other AR antagonists such as Flutamide, Casodex, Nilutamide, or Cyproterone acetate.

The present invention provides compounds which can be used to treat patients suffering from prostate cancer resistant to androgen receptor antagonists which are not within formula I of the invention (or salts thereof), such as bicalutimide. The invention thus further contemplates a method of treating prostate cancer resistant to an androgen receptor antagonist other than those of formula I or salts thereof, comprising the step of administering to a patient in need thereof a compound capable of reducing the growth rate of the tumor mass of said cancer in an amount effective therefor. The term "reducing the growth rate of said tumor mass" denotes reduction in the growth rate (including, of course, stabilization or reduction in size) of said tumor mass upon treatment relative to the growth rate upon treatment with said androgen receptor antagonist other than those of formula I or salts thereof. Compounds of the formula I and pharmaceutically acceptable salts thereof of the present invention are preferred such compounds.

The present invention also contemplates use of an antiestrogen and/or aromatase inhibitor in combination with a compound of the present invention, for example, to assist in mitigating side effects associated with antiandrogen therapy such as gynecomastia. Exemplary antiestrogen and/or aromatase inhibitors include anastrozole (Arimidex), tamoxifen citrate (Nolvadex), exemestane (Aromasin), toremifene citrate (Fareston), letrozole (Femara), raloxifene hydrochloride (Evista), Faslodex, or 923 (Wyeth Ayerst).

The compounds of the present invention may be employed adjunct to surgery.

Another application of the present compounds is in combination with antibody therapy such as but not limited to antibody therapy against PSCA. An additional application is in concert with vaccine / immune modulating agents for the treatment of cancer.

- 5           Compounds of the present invention can be employed in accordance with the methods described in U.S. Provisional Patent Application Serial No. 60/284,438, entitled "Selective Androgen Receptor Modulators and Methods for Their Identification, Design and Use" filed April 18, 2001 by Mark E. Salvati *et al.* (Attorney Docket No. LD0250(PSP)), which Provisional Patent Application is
- 10   incorporated herein by reference in its entirety (including, but not limited to, reference to all specific compounds within formula I of the present invention), and U.S. Patent Application Serial No. 09/885,827, entitled "Selective Androgen Receptor Modulators and Methods for Their Identification, Design and Use" filed June 20, 2001 by Mark E. Salvati *et al.* (Attorney Docket No. LD0250(NP)), which Patent
- 15   Application is incorporated herein by reference in its entirety (including, but not limited to, reference to all specific compounds within formula I of the present invention).

- For racemates of compounds of the present invention, one enantiomer can, for example be a full AR antagonist while the other can be an AR antagonist in tumor
- 20   tissue while having no activity or agonist activity in nontumor tissue containing the androgen receptor.

- The above other therapeutic agents, when employed in combination with the compounds of the present invention, can be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one
- 25   of ordinary skill in the art.

- The following assays can be employed in ascertaining the activity of a compound as a NHR modulator. Preferred are those compounds with an activity greater than 20 $\mu$ m for binding or transactivation in any of these assays. Various compounds of the present invention were determined to have AR modulator activity
- 30   utilizing the transactivation assay, and standard AR binding assays as described following.

**Transactivation Assays:****AR Specific Assay:**

5           Compounds of the present invention were tested in transactivation assays of  
a transfected reporter construct and using the endogenous androgen receptor of the  
host cells. The transactivation assay provides a method for identifying functional  
agonists and partial agonists that mimic, or antagonists that inhibit, the effect of native  
hormones, in this case, dihydrotestosterone (DHT). This assay can be used to predict  
10 *in vivo* activity as there is a good correlation in both series of data. See, e.g. T. Berger  
et al., *J. Steroid Biochem. Molec. Biol.* 773 (1992), the disclosure of which is herein  
incorporated by reference.

For the transactivation assay a reporter plasmid is introduced by  
transfection (a procedure to induce cells to take foreign genes) into the respective  
15 cells. This reporter plasmid, comprising the cDNA for a reporter protein, such as  
secreted alkaline phosphatase (SEAP), controlled by prostate specific antigen (PSA)  
upstream sequences containing androgen response elements (AREs). This reporter  
plasmid functions as a reporter for the transcription-modulating activity of the AR.  
Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally  
20 expressed by a gene under control of the AR and its native hormone. In order to  
detect antagonists, the transactivation assay is carried out in the presence of constant  
concentration of the natural AR hormone (DHT) known to induce a defined reporter  
signal. Increasing concentrations of a suspected antagonist will decrease the reporter  
signal (e.g., SEAP production). On the other hand, exposing the transfected cells to  
25 increasing concentrations of a suspected agonist will increase the production of the  
reporter signal.

For this assay, LNCaP and MDA 453 cells were obtained from the  
American Type Culture Collection (Rockville, MD), and maintained in RPMI 1640 or  
DMEM medium supplemented with 10% fetal bovine serum (FBS; Gibco)  
30 respectively. The respective cells were transiently transfected by electroporation  
according to the optimized procedure described by Heiser, 130 Methods Mol. Biol.,  
117 (2000), with the pSEAP2/PSA540/Enhancer reporter plasmid. The reporter

plasmid, was constructed as follows: commercial human placental genomic DNA was used to generate by Polymerase Cycle Reaction (PCR) a fragment containing the BglII site (position 5284) and the Hind III site at position 5831 of the human prostate specific antigen promoter (Accession # U37672), Schuur, et al., *J. Biol. Chem.*, **271** (12): 7043-51 (1996). This fragment was subcloned into the pSEAP2/basic (Clontech) previously digested with BglII and HindIII to generate the pSEAP2/PSA540 construct. Then a fragment bearing the fragment of human PSA upstream sequence between positions -5322 and -3873 was amplified by PCR from human placental genomic DNA. A XhoI and a BglII sites were introduced with the primers. The resulting fragment was subcloned into pSEAP2/PSA540 digested with XhoI and BglII respectively, to generate the pSEAP2/PSA540/Enhancer construct. LNCaP and MDA 453 cells were collected in media containing 10% charcoal stripped FBS. Each cell suspension was distributed into two Gene Pulser Cuvetts (Bio-Rad) which then received 8 µg of the reporter construct, and electoporated using a Bio-Rad Gene Pulser at 210 volts and 960 µFaraday. Following the transfections the cells were washed and incubated with media containing charcoal stripped fetal bovine serum in the absence (blank) or presence (control) of 1 nM dihydrotestosterone (DHT; Sigma Chemical) and in the presence or absence of the standard anti-androgen bicalutamide or compounds of the present invention in concentrations ranging from 10<sup>-10</sup> to 10<sup>-5</sup> M (sample). Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory workstation. After 48 hours, a fraction of the supernatant was assayed for SEAP activity using the Phospha-Light Chemiluminescent Reporter Gene Assay System (Tropix, Inc). Viability of the remaining cells was determined using the CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (MTS Assay, Promega). Briefly, a mix of a tetrazolium compound (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt; MTS) and an electron coupling reagent (phenazine methosulfate; PMS) are added to the cells. MTS (Owen's reagent) is bioreduced by cells into a formazan that is soluble in tissue culture medium, and therefore its absorbance at 490nm can be measured directly from 96 well assay plates without additional processing. The quantity of formazan product as measured by the amount of 490nm absorbance is directly proportional to the number of living cells in

culture. For each replicate the SEAP reading was normalized by the Abs490 value derived from the MTS assay. For the antagonist mode, the % Inhibition was calculated as:

$$5 \quad \% \text{ Inhibition} = 100 \times (1 - [\text{average control} - \text{average blank} / \text{average sample} - \text{average blank}])$$

Data was plotted and the concentration of compound that inhibited 50% of the normalized SEAP was quantified ( $IC_{50}$ ).

10

For the agonist mode % Control was referred as the effect of the tested compound compared to the maximal effect observed with the natural hormone, in this case DHT, and was calculated as:

$$15 \quad \% \text{ Control} = 100 \times \text{average sample} - \text{average blank} / \text{average control} - \text{average blank}$$

Data was plotted and the concentration of compound that activates to levels 50% of the normalized SEAP for the control was quantified ( $EC_{50}$ ).

## 20 **GR Specificity Assay:**

- The reporter plasmid utilized was comprised of the cDNA for the reporter SEAP protein, as described for the AR specific transactivation assay. Expression of the reporter SEAP protein was controlled by the mouse mammary tumor virus long terminal repeat (MMTV LTR) sequences that contains three hormone response elements (HREs) that can be regulated by both GR and PR see, e.g. G. Chalepakis et al., Cell, 53(3), 371 (1988). This plasmid was transfected into A549 cells, which expresses endogenous GR, to obtain a GR specific transactivation assay. A549 cells were obtained from the American Type Culture Collection (Rockville, MD), and maintained in RPMI 1640 supplemented with 10% fetal bovine serum (FBS; Gibco).
- 30 Determination of the GR specific antagonist activity of the compounds of the present invention was identical to that described for the AR specific transactivation assay, except that the DHT was replaced with 5 nM dexamethasone (Sigma Chemicals), a

specific agonist for GR. Determination of the GR specific agonist activity of the compounds of the present invention was performed as described for the AR transactivation assay, wherein one measures the activation of the GR specific reporter system by the addition of a test compound, in the absence of a known GR specific agonists ligand.

#### **PR Specific Assay:**

The reporter plasmid utilized was comprised of the cDNA for the reporter SEAP protein, as described for the AR specific transactivation assay.

- 10 Expression of the reporter SEAP protein was controlled by the mouse mammary tumor virus long terminal repeat (MMTV LTR) sequences that contains three hormone response elements (HREs) that can be regulated by both GR and PR. This plasmid was transfected into T47D, which expresses endogenous PR, to obtain a PR specific transactivation assay. T47D cells were obtained from the American Type Culture Collection (Rockville, MD), and maintained in DMEM medium supplemented with 10% fetal bovine serum (FBS; Gibco). Determination of the PR specific antagonist activity of the compounds of the present invention was identical to that described for the AR specific transactivation assay, except that the DHT was replaced with 1 nM Promegestone (NEN), a specific agonist for PR. Determination of
- 20 the PR specific agonist activity of the compounds of the present invention was performed as described for the AR transactivation assay, wherein one measures the activation of the PR specific reporter system by the addition of a test compound, in the absence of a known PR specific agonists ligand.

#### **25 AR Binding Assay:**

For the whole cell binding assay, human LNCaP cells (T877A mutant AR) or MDA 453 (wild type AR) in 96-well microtiter plates containing RPMI 1640 or DMEM supplemented with 10% charcoal stripped CA-FBS (Cocaleco Biologicals) respectively, were incubated at 37°C to remove any endogenous ligand that might be

30 complexed with the receptor in the cells. After 48 hours, either a saturation analysis to determine the  $K_d$  for tritiated dihydrotestosterone, [ $^3\text{H}$ ]-DHT, or a competitive binding assay to evaluate the ability of test compounds to compete with [ $^3\text{H}$ ]-DHT

were performed. For the saturation analysis, media (RPMI 1640 or DMEM – 0.2% CA-FBS) containing [ $^3$ H]-DHT (in concentrations ranging from 0.1 nM to 16 nM) in the absence (total binding) or presence (non-specific binding) of a 500-fold molar excess of unlabeled DHT were added to the cells. After 4 hours at 37°C, an aliquot of the total binding media at each concentration of [ $^3$ H]-DHT was removed to estimate the amount of free [ $^3$ H]-DHT. The remaining media was removed, cells were washed three times with PBS and harvested onto UniFilter GF/B plates (Packard), Microscint (Packard) was added and plates counted in a Top-Counter (Packard) to evaluate the amount of bound [ $^3$ H]-DHT.

For the saturation analysis, the difference between the total binding and the non-specific binding, was defined as specific binding. The specific binding was evaluated by Scatchard analysis to determine the  $K_d$  for [ $^3$ H]-DHT. See e.g. D. Rodbard, Mathematics and statistics of ligand assays: an illustrated guide: In: J. Langon and J. J. Clapp, eds., Ligand Assay, Masson Publishing U.S.A., Inc., New York, pp. 45-99, (1981), the disclosure of which is herein incorporated by reference.

For the competition studies, media containing 1 nM [ $^3$ H]-DHT and compounds of the invention ("test compounds") in concentrations ranging from  $10^{-10}$  to  $10^{-5}$  M were added to the cells. Two replicates were used for each sample. After 4 hours at 37°C, cells were washed, harvested and counted as described above. The data was plotted as the amount of [ $^3$ H]-DHT (% of control in the absence of test compound) remaining over the range of the dose response curve for a given compound. The concentration of test compound that inhibited 50% of the amount of [ $^3$ H]-DHT bound in the absence of competing ligand was quantified ( $IC_{50}$ ) after log-logit transformation. The  $K_i$  values were determined by application of the Cheng-Prusoff equation to the  $IC_{50}$  values, where:

$$K_i = \frac{IC_{50}}{(1 + (^3H\text{-DHT}) / K_d \text{ for } ^3H\text{-DHT})}$$

After correcting for non-specific binding,  $IC_{50}$  values were determined. The  $IC_{50}$  is defined as the concentration of competing ligand needed to reduce specific binding by 50%. The  $K_d$ s for [ $^3$ H]-DHT for MDA 453 and LNCaP were 0.7 and 0.2 nM respectively.



**Human Prostate Cell Proliferation Assay:**

Compounds of the present invention were tested ("test compounds") on the proliferation of human prostate cancer cell lines. For that, MDA PCa2b cells, a cell line derived from the metastasis of a patient that failed castration, Navone et al., *Clin. Cancer Res.*, **3**, 2493-500 (1997), were incubated with or without the test compounds for 72 hours and the amount of [<sup>3</sup>H]-thymidine incorporated into DNA was quantified as a way to assess number of cells and therefore proliferation. The MDA PCa2b cell line was maintained in BRFF-HPC1 media (Biological Research Faculty & Facility Inc., MD) supplemented with 10% FBS. For the assay, cells were plated in Biocoated 96-well microplates and incubated at 37°C in 10% FBS (charcoal-stripped)/BRFF-BMZERO (without androgens). After 24 hours, the cells were treated in the absence (blank) or presence of 1 nM DHT (control) or with test compounds (sample) of the present invention in concentrations ranging from 10<sup>-10</sup> to 10<sup>-5</sup> M. Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory work station. Seventy two hours later 0.44 uCi. of [<sup>3</sup>H]-Thymidine (Amersham) was added per well and incubated for another 24 h followed by tripsinization, harvesting of the cells onto GF/B filters. Micro-scent PS were added to the filters before counting them on a Beckman TopCount.

The % Inhibition was calculated as:

$$\% \text{ Inhibition} = 100 \times (1 - [\text{average control} - \text{average blank} / \text{average sample} - \text{average blank}])$$

Data was plotted and the concentration of compound that inhibited 50% of the [<sup>3</sup>H]-Thymidine incorporation was quantified (IC<sub>50</sub>).

**C2C12 Mouse Myoblast Transactivation Assay:**

Two functional transactivation assays were developed to assess the efficacy of androgen agonists in a muscle cell background using a luciferase reporter. The first assay (ARTA Stable 1) uses a cell line, Stable 1 (clone #72), which stably expresses the full length rat androgen receptor but requires the transient transfection of an enhancer/reporter. This cell line was derived from C2C12 mouse myoblast cells. The second assay (ARTA Stable 2) uses a cell line, Stable 2 (clone #133), derived from Stable 1 which stably expresses both rAR and the enhancer/luciferase reporter.

The enhancer/reporter construct used in this system is pGL3/2XDR-1/luciferase. 2XDR-1 was reported to be an AR specific response element in CV-1 cells, Brown et. al. *The Journal of Biological Chemistry* **272**, 8227-8235, (1997). It was developed by random mutagenesis of an AR/GR consensus enhancer sequence.

5

**ARTA Stable 1:**

1. Stable 1 cells are plated in 96 well format at 6,000 cells/well in high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1X MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5X Antibiotic-Antimycotic, and 800 µg/ml Geneticin (Gibco BRL, Cat. No.: 10131-035).
2. 48 hours later, cells are transfected with pGL3/2XDR-1/luciferase using LipofectAMINE Plus™ Reagent (Gibco BRL, Cat. No.: 10964-013).
- 15 Specifically, 5 ng/well pGL3/2XDR-1/luciferase DNA and 50 ng/well Salmon Sperm DNA (as carrier) are diluted with 5 µl/well Opti-MEM media (Gibco BRL, Cat. No.: 31985-070). To this, 0.5 µl/well Plus reagent is added. This mixture is incubated for 15 minutes at room temperature. In a separate vessel, 0.385 µl/well LipofectAMINE reagent is diluted with 5 µl/well Opti-MEM. The
- 20 DNA mixture is then combined with the LipofectAMINE mixture and incubated for an additional 15 minutes at room temperature. During this time, the media from the cells is removed and replaced with 60 µl/well of Opti-MEM. To this is added 10 µl/well of the DNA/LipofectAMINE transfection mixture. The cells are incubated for 4 hours.
- 25 3. The transfection mixture is removed from the cells and replaced with 90 µl of media as in #1 above.
4. 10 µl/well of appropriate drug dilution is placed in each well.
5. 24 hours later, the Steady-Glo™ Luciferase Assay System is used to detect activity according to the manufacturer's instructions (Promega, Cat. No.: E2520).

30

**ARTA stable 2**

1. Stable 2 cells are plated in 96 well format at 6,000 cells/well in high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM
- 5 HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1X MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5X Antibiotic-Antimycotic, 800 µg/ml Geneticin (Gibco BRL, Cat. No.: 10131-035) and 800 µg/ml Hygromycin β (Gibco BRL, Cat. No.: 10687-010).
2. 48 hours later, the media on the cells is removed and replaced with 90 µl fresh. 10
- 10 µl/well of appropriate drug dilution is placed in each well.
3. 24 hours later, the Steady-Glo™ Luciferase Assay System is used to detect activity according to the manufacturer's instructions (Promega, Cat. No.: E2520).

- See U.S. Patent Application Serial No. 09/885,831, entitled "Cell Lines and Cell-Based Assays for Identification of Androgen Receptor Modulators" filed June 20, 2001 by Jacek Ostrowski *et al.* (Attorney Docket No. D0177), which Patent Application is incorporated herein by reference in its entirety.

**Proliferation Assays****20 Murine Breast Cell Proliferation Assay:**

- The ability of compounds of the present invention ("test compounds") to modulate the function of the AR was determined by testing said compounds in a proliferation assay using the androgen responsive murine breast cell line derived from the Shionogi tumor, Hiraoka *et al.*, *Cancer Res.*, **47**, 6560-6564 (1987). Stable AR
- 25 dependent clones of the parental Shionogi line were established by passing tumor fragments under the general procedures originally described in Tetuo, *et al.*, *Cancer Research* **25**, 1168-1175 (1965). From the above procedure, one stable line, SC114, was isolated, characterized and utilized for the testing of example compounds. SC114 cells were incubated with or without the test compounds for 72 hours and the amount
- 30 of [3H]-thymidine incorporated into DNA was quantified as a surrogate endpoint to assess the number of cells and therefore the proliferation rate as described in Suzuki *et al.*, *J. Steroid Biochem. Mol. Biol.* **37**, 559-567 (1990). The SC114 cell line was

maintained in MEM containing  $10^{-8}$  M testosterone and 2% DCC-treated FCS. For the assay, cells were plated in 96-well microplates in the maintenance media and incubated at 37°C. On the following day, the medium was changed to serum free medium [Ham's F-12:MEM (1;1, v/v) containing 0.1% BSA] with (antagonist mode) or without (agonist mode)  $10^{-8}$  M testosterone and the test compounds of the present invention in concentrations ranging from  $10^{-10}$  to  $10^{-5}$  M. Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory work station. Seventy two hours later 0.44uCi of [3H]-Thymidine (Amersham) was added per well and incubated for another 2 hr followed by trypsinization, and harvesting of the cells onto GF/B filters. Micro-scint PS were added to the filters before counting them on a Beckman TopCount.

For the antagonist mode, the % Inhibition was calculated as:

$$\% \text{ Inhibition} = 100 \times (1 - [\text{average sample} - \text{average blank} / \text{average control} - \text{average blank}])$$

Data was plotted and the concentration of compound that inhibited 50% of the [ $^3$ H]-Thymidine incorporation was quantified ( $IC_{50}$ ).

For the agonist mode % Control was referred as the effect of the tested compound compared to the maximal effect observed with the natural hormone, in this case DHT, and was calculated as:

$$\% \text{ Control} = 100 \times (\text{average sample} - \text{average blank}) / (\text{average control} - \text{average blank})$$

Data was plotted and the concentration of compound that inhibited 50% of the [ $^3$ H]-Thymidine incorporation was quantified ( $EC_{50}$ ).

#### **In Vitro Assay to Measure GR Induced AP-1 Transrepression:**

The AP-1 assay is a cell based luciferase reporter assay. A549 cells, which contain endogenous glucocorticoid receptor, were stably transfected with an AP-1 DNA binding site attached to the luciferase gene. Cells are

then grown in RPMI + 10% fetal calf serum (charcoal-treated) + Penicillin/Streptomycin with 0.5mg/ml geneticin. Cells are plated the day before the assay at approximately 40000 cells/well. On assay day, the media is removed by aspiration and 20  $\mu$ l assay buffer (RPMI without phenol red + 10% FCS (charcoal-treated) + Pen/Strep) is added to each well. At this point either 20  $\mu$ l assay buffer (control experiments), the compounds of the present invention ("test compounds") (dissolved in DMSO and added at varying concentrations) or dexamethasone (100 nM in DMSO, positive control) are added to each well. The plates are then pre-incubated for 15 minutes at 37°C, followed by stimulation of the cells with 10 ng/ml PMA. The plates are then incubated for 7 hrs at 37°C after which 40  $\mu$ l luciferase substrate reagent is added to each well. Activity is measured by analysis in a luminometer as compared to control experiments treated with buffer or dexamethasone. Activity is designated as % inhibition of the reporter system as compared to the buffer control with 10 ng/ml PMA alone. The control, dexamethasone, at a concentration of  $\leq 10$   $\mu$ M typically suppresses activity by 65%. Test compounds which demonstrate an inhibition of PMA induction of 50% or greater at a concentration of test compound of  $\leq 10$   $\mu$ M are deemed active.

#### **Wet Prostate Weight Assay AR Antagonist Assay:**

The activity of compounds of the present invention as AR antagonists was investigated in an immature male rat model, a standard, recognized test of antiandrogen activity of a given compound, as described in L. G. Hersherberger et al., *Proc. Soc. Expt. Biol. Med.*, **83**, 175 (1953); P. C. Walsh and R. F. Gittes, "Inhibition of extratesticular stimuli to prostate growth in the castrated rat by antiandrogens", *Endocrinology*, **86**, 624 (1970); and B. J. Furr et al., "ICI 176,334: A novel non-steroid, peripherally selective antiandrogen", *J. Endocrinol.*, **113**, R7-9 (1987), the disclosures of which are herein incorporated by reference.

The basis of this assay is the fact that male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function.

These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH).

- 5 Testosterone is converted to the more active form, dihydrotestosterone, (DHT), within the prostate by  $5\alpha$ -reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, compared to 40% of that in 65-year-old men. F. Labrie et al. Clin. Invest. Med., **16**, 475-492 (1993). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the
- 10 prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostate tissues. M. C. Luke and D. S. Coffey, "*The Physiology of Reproduction*" ed. By E. Knobil and J. D. Neill, **1**, 1435-1487 (1994). Since the male sex organs are the tissues most responsive to modulation of the androgen activity, this model is used to determine the
- 15 androgen dependent growth of the sex accessory organs in immature castrated rats.

- Male immature rats (19-20 days old Sprague-Dawley, Harlan Sprague-Dawley) were castrated under metofane anesthesia. Five days after surgery these castrated rats (60-70g, 23-25 day-old) were dosed for 3 days. Animals were dosed sub-cutaneously (s.c.) 1mg/kg with Testosterone Propionate (TP) in arachis oil
- 20 vehicle and anti-androgen test compounds (compounds of the present invention) were dosed orally by gavage (p.o.) in dissolved/suspensions of 80% PEG 400 and 20% Tween 80 (PEGTW). Animals were dosed (v/w) at 0.5 ml of vehicle /100g body weight. Experimental groups were as follows:

1. Control vehicle
- 25 2. Testosterone Propionate (TP) (3 mg/rat/day, subcutaneous)
3. TP plus Casodex (administered p.o. in PEGTW, QD) , a recognized antiandrogen, as a reference compound.
4. To demonstrate antagonist activity, a compound of the present invention ("test compound") was administered (p.o. in PEGTW, QD) with TP (s.c. as
- 30 administered in group 2) in a range of doses.

5. To demonstrate agonist activity a compound of the present invention ("test compound") was administered alone (p.o. in PEGTW, QD) in a range of doses.

At the end of the 3-day treatment, the animals were sacrificed, and the ventral prostate weighed. To compare data from different experiments, the sexual organs weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase (100%). ANOVA followed by one-tailed Student or Fischer's exact test was used for statistical analysis.

- 10 The gain and loss of sexual organ weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration. See Y. Okuda et al., *J. Urol.*, **145**, 188-191 (1991), the disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In immature castrated rats, replacement of exogenous androgens increases seminal vesicles (SV) and the ventral prostate (VP) in a dose dependent manner.

- The maximum increase in organ weight was 4 to 5-fold when dosing 3 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days. The EC<sub>50</sub> of T and TP were about 1 mg and 0.03 mg, respectively. The increase in the weight of the VP and SV also correlated with the increase in the serum T and DHT concentration. Although administration of T showed 5-times higher serum concentrations of T and DHT at 2 hours after subcutaneous injection than that of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 24 hours, and therefore, TP showed about 10-30-fold higher potency than free T.

- In this immature castrated rat model, a known AR antagonist (Casodex) was also administered simultaneously with 0.1 mg of TP (ED<sub>80</sub>), inhibiting the testosterone-mediated increase in the weights of the VP and SV in a dose dependent manner. The antagonist effects were similar when dosing orally or subcutaneously. Compounds of the invention also exhibited AR antagonist activity by suppressing the testosterone-mediated increase in the weights of VP and SV.

**Levator Ani & Wet Prostate Weight Assay AR Agonist Assay:**

The activity of compounds of the present invention as AR agonists was investigated in an immature male rat model, a recognized test of anabolic effects in muscle and sustaining effects in sex organs for a given compound, as described in L.

- 5 G. Hershberger et al., *Proc. Soc. Expt. Biol. Med.*, **83**, 175 (1953); B. L. Beyler et al., "Methods for evaluating anabolic and catabolic agents in laboratory animals", *J. Amer. Med. Women's Ass.*, **23**, 708 (1968); H. Fukuda et al., "Investigations of the levator ani muscle as an anabolic steroid assay", *Nago Dai. Yak. Ken. Nem.* **14**, 84 (1966) the disclosures of which are herein incorporated by reference.
- 10 The basis of this assay lies in the well-defined action of androgenic agents on the maintenance and growth of muscle tissues and sexual accessory organs in animals and man. Androgenic steroids, such as testosterone (T), have been well characterized for their ability to maintain muscle mass. Treatment of animals or humans after castrations with an exogenous source of T results in a reversal of muscular atrophy.
- 15 The effects of T on muscular atrophy in the rat levator ani muscle have been well characterized. M. Masuoka et al., "Constant cell population in normal, testosterone deprived and testosterone stimulated levator ani muscles" *Am. J. Anat.* **119**, 263 (1966); Z. Gori et al., "Testosterone hypertrophy of levator ani muscle of castrated rats. I. Quantitative data" *Boll. -Soc. Ital. Biol. Sper.* **42**, 1596 (1966); Z. Gori et al.,
- 20 "Testosterone hypertrophy of levator ani muscle of castrated rats. II. Electron-microscopic observations" *Boll. -Soc. Ital. Biol. Sper.* **42**, 1600 (1966); A. Boris et al., *Steroids* **15**, 61 (1970). As described above, the effects of androgens on maintenance of male sexual accessory organs, such as the prostate and seminal vesicles, is well described. Castration results in rapid involution and atrophy of the
- 25 prostate and seminal vesicles. This effect can be reversed by exogenous addition of androgens. Since both the levator ani muscle and the male sex organs are the tissues most responsive to the effects of androgenic agents, this model is used to determine the androgen dependent reversal of atrophy in the levator ani muscle and the sex accessory organs in immature castrated rats. Sexually mature rats (200-250 g, 6-8
- 30 weeks-old, Sprague-Dawley, Harlan) were acquired castrated from the vendor (Taconic). The rats were divided into groups and treated daily for 7 to 14 days with one of the following:



1. Control vehicle
2. Testosterone Propionate (TP) (3 mg/rat/day, subcutaneous)
3. TP plus Casodex (administered p.o. in PEGTW, QD), a recognized antiandrogen, as a reference compound.
- 5 4. To demonstrate antagonist activity, a compound of the present invention ("test compound") was administered (p.o. in PEGTW, QD) with TP (s.c. as administered in group 2) in a range of doses.
5. To demonstrate agonist activity a compound of the present invention ("test compound") was administered alone (p.o. in PEGTW, QD) in a range of
- 10 doses.

At the end of the 7-14-day treatment, the animals were sacrificed by carbon dioxide, and the levator ani, seminal vesicle and ventral prostate weighed. To compare data from different experiments, the levator ani muscle and sexual organ weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase (100%).

15 Super-anova (one factor) was used for statistical analysis.

The gain and loss of sexual organ weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration. See Y. Okuda et al., *J. Urol.*, **145**, 188-191 (1991), the

20 disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In immature castrated rats, replacement of exogenous androgens increases levator ani, seminal vesicles (SV) and prostate in a dose dependent manner.

The maximum increase in organ weight was 4 to 5-fold when dosing 3

25 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days. The EC<sub>50</sub> of T and TP were about 1 mg and 0.03 mg, respectively. The increase in the weight of the VP and SV also correlated with the increase in the serum T and DHT concentration. Although administration of T showed 5-times higher serum concentrations of T and DHT at 2 hours after subcutaneous injection than that

30 of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 24 hours, and therefore, TP showed about 10-30-fold higher potency than free T.

**MDA PCa2b Human Prostate Xenograft Assay:**

- In Vivo Antitumor Testing: MDA-PCa-2b human prostate tumors were maintained in Balb/c nu/nu nude mice. Tumors were propagated as subcutaneous
- 5 transplants in adult male nude mice (4-6 weeks old) using tumor fragments obtained from donor mice. Tumor passage occurred every 5-6 weeks.

- For antitumor efficacy trial, the required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (~50 mg) with a 13-gauge trocar. Tumors
- 10 were allowed to grow to approx. 100-200 mg (tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation of treatment (Wt1) and then again
- 15 following the last treatment dose (Wt2). The difference in body weight (Wt2-Wt1) provides a measure of treatment-related toxicity.

- Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reach a predetermined "target" size of 0.5 gm. Tumor weights (mg) were estimated from the formula: Tumor weight = (length x width<sup>2</sup>) ÷ 2
- 20 Tumor response end-point was expressed in terms of tumor growth inhibition (%T/C), defined as the ratio of median tumor weights of the treated tumors (T) to that of the control group (C).

- To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:
- 25 TVDT = Median time (days) for control tumors to reach target size – Median time (days) for control tumors to reach half the target size s
- And, Log cell kill = (T-C) ÷ (3.32 x TVDT)

- Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test.

30 **Dunning Prostate Tumor:**

Dunning R3327H prostate tumor is a spontaneously derived, well differentiated androgen responsive adenocarcinoma of the prostate

(Smolev JK, Heston WD, Scott WW, and Coffey DS, *Cancer Treat Rep.* **61**, 273-287 (1977)). The growth of the R3327H subline has been selected for its highly androgen-dependent and reproducible growth in intact male rats. Therefore, this model and other sublines of this tumor have been

5 widely used to evaluate *in vivo* antitumor activities of antiandrogens such as flutamide and bicalutamide/Casodex (Maucher A., and von Angerer, J. *Cancer Res. Clin. Oncol.*, **119**, 669-674 (1993), Furr B.J.A. *Euro. URL.* **18** (suppl. 3), 2-9 (1990), Shain S.A. and Huot R.I. *J. Steroid Biochem.* **31**, 711-718 (1988)).

- 10 At the beginning of the study, the Dunning tumor pieces (about 4 x 4 mm) are transplanted subcutaneously to the flank of mature male Copenhagen rats (6-7 weeks old, Harlan-Sprague Dawley, Indianapolis, MD). About 6 weeks after the implantation, the animals with tumors of measurable size (about 80 - 120 mm<sup>3</sup>) are randomized into treatment
- 15 groups (8-10 rats/group) and the treatments are initiated. One group of the rats are castrated to serve as the negative control of tumor growth. Animals are treated daily with compounds of the current invention, standard antiandrogens such as bicalutamide or vehicle (control) for an average of 10 to 14 weeks. Test compounds are dissolved in a vehicle of
- 20 (2.5 ml/kg of body weight) 10% polyethylene glycol and 0.05% Tween-80 in 1% carboxymethyl cellulose, PEG/CMC, (Sigma, St Louis, MO). Typical therapeutic experiments would include three groups of three escalating doses for each standard or test compound (in a range of 300-3 mg/kg).

- Tumors in the vehicle (control) group reach a size of 1500 to 2500 mm<sup>3</sup>,
- 25 whereas the castrated animal group typically shows tumor stasis over the 14 weeks of observation. Animals treated orally with 20 mg/kg of bicalutamide or flutamide would be expected to show a 40% reduction in tumor volumes compared to control after 14 weeks of treatment. The size of tumors are measured weekly by vernier caliper (Froboz, Switzerland), taking perpendicular measurements of length and
- 30 width. Tumor volumes are measured in mm<sup>3</sup> using the formula: Length x Width x Height = Volume. Statistical differences between treatment groups and control are

evaluated using multiple ANOVA analysis followed by one tail non-parametric Student t test.

**Mature Rat Prostate Weight Assay:**

- 5           The activity of compounds of the present invention were investigated in a mature male rat model, which is a variation of the Levator ani & wet prostate weight assay described above. The above *in vivo* assays are recognized assays for determining the anabolic effects in muscle and sustaining effects in sex organs for a given compound, as described in L. G. Hershberger *et al.*, 83 *Proc. Soc. Expt. Biol. Med.*, 175 (1953); B. L. Beyler *et al.*, "Methods for evaluating anabolic and catabolic agents in laboratory animals", 23 *J. Amer. Med. Women's Ass.*, 708 (1968); H. Fukuda *et al.*, "Investigations of the levator ani muscle as an anabolic steroid assay", 14 *Nago Dai. Yak. Ken. Nem.* 84 (1966) the disclosures of which are herein incorporated by reference. The basis of this assay lies in the well-defined action of androgenic agents
  - 15   on the maintenance and growth of muscle tissues and sexual accessory organs in animals and man.
- The male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and secretory function by the continued presence
- 20   of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone, (DHT), within the prostate by 5 $\alpha$ -reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, compared to
  - 25   40% of that in 65-year-old men. F. Labrie *et. al.* 16 *Clin. Invest. Med.*, 475-492 (1993). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostate tissues, M. C. Luke and D. S.
  - 30   Coffey, "The Physiology of Reproduction" ed. By E. Knobil and J. D. Neill, 1, 1435-1487 (1994). Since the male sex organs and the levator ani are the tissues most

responsive to modulation of the androgen activity, this model is used to determine the activity of compounds that modulate the androgen receptor pathway in mature rats.

Along with its mitogenic activity on tissues such as prostate, seminal vesicle and muscle, testosterone also serves as a negative regulator for its own biosynthesis. Testosterone production in the Leydig cells of the testis is controlled by the level of circulating LH released from the pituitary gland. LH levels are themselves controlled by the level of LHRH produced in the hypothalamic region. Testosterone levels in the blood serve to inhibit the secretion of LHRH and subsequently reduce levels of LH and ultimately the levels of circulating testosterone levels. By measuring blood levels of LH as they are effected by compounds of the present invention ("test compounds"), it is possible to determine the level of agonist or antagonist activity of said compounds at the hypothalamic axis of this endocrine cycle.

Matched sets of Harlan Sprague-Dawely rats (40-42 days old, 180-220 g), were dosed orally by gavage (p.o.) with the test compounds in dissolved/suspensions of 80% PEG 400 and 20% Tween 20 (PEGTW) for 14 days. Two control groups, one intact and one castrated were dose orally only with the PEGTW vehicle. Animals were dosed (v/w) at 0.5 ml of vehicle /100g body weight. Experimental groups were as follows:

1. Intact vehicle (p.o., PEGTW, QD)
2. Control vehicle (p.o., PEGTW, QD)
3. Bicalutamide (Casodex, a recognized antiandrogen, as a reference compound) or a compound of the present invention, p.o. in PEGTW QD. (in a range of doses).

At the end of the 14-day treatment, the animals were sacrificed, and the ventral prostate, the seminal vesicles, and the levator ani were removed surgically and weighed. To compare data from different experiments, the organs weights were first standardized as mg per 100 g of body weight, and expressed as a percentage of the value of the respective organ in the intact group.

Rat luteinizing hormone (rLH) is quantitatively determined with the Biotrak [125 I] kit (Amersham Pharmacia Biotech), following the manufacturer directions. The assay is based on the competition by the LH present in the serum of the binding of [<sup>125</sup>I] rLH to an Amerlex-M bead/antibody suspension. The radioactivity that

remains after incubation with the serum and subsequent washes is extrapolated into a standard curve to obtain a reading in ng/ml.

The gain and loss of sexual organ and levator ani weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration, see Y. Okuda *et al.*, *J. Urol.*, **145**, 188-191 (1991), the disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In the mature rats assay, active agonist agents will have no effect or will increase the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a suppressive effect on LH secretion. Compounds with antagonist activity will decrease the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a reduced suppressive effect on LH secretion.

**15    CWR22 Human Prostate Xenograft Assay:**

*In Vivo* Antitumor Testing: CWR22 human prostate tumors were maintained in Balb/c nu/nu nude mice. Tumors were propagated as subcutaneous transplants in adult male nude mice (4-6 weeks old) using tumor fragments obtained from donor mice. Tumor passage occurred every 5-6 weeks.

20        For antitumor efficacy trial, the required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (~50 mg) with a 13-gauge trocar. Tumors were allowed to grow to approx. 100-200 mg (tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2-Wt1) provides a measure of treatment-related toxicity.

25

30

Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reach a predetermined "target" size of 0.5 gm. Tumor weights (mg) were estimated from the formula: Tumor weight = (length x width<sup>2</sup>) ÷ 2.

- 5 Tumor response end-point was expressed in terms of tumor growth inhibition (%T/C), defined as the ratio of median tumor weights of the treated tumors (T) to that of the control group (C).

To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:

- 10 TVDT = Median time (days) for control tumors to reach target size –  
Median time (days) for control tumors to reach half the target size  
And, Log cell kill = (T-C) ÷ (3.32 x TVDT)

Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test.

15

The following Examples illustrate embodiments of the present invention, and are not intended to limit the scope of the claims. Within certain Examples, one compound of the formula I is prepared and then employed to further prepare one or more additional compounds of the formula I or salts thereof. Methods employed to  
20 prepare one compound of the formula I or salt thereof as described herein can be employed as appropriate to prepare other compounds of the invention.

Abbreviations

The following abbreviations are used herein:

	DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
	4-DMAP = 4-dimethylaminopyridine
5	ee = enantiomeric excess
	DMF = dimethylformamide
	EtOAc = ethyl acetate
	LDA = lithium diisopropylamide
	Hünig's Base = N,N-diisopropylethylamine
10	Me = methyl
	RT = retention time
	TFA = trifluoroacetic acid
	THF = tetrahydrofuran
	TLC = thin layer chromatography
15	TMS = trimethylsilyl
	pTSA = para-toluenesulfonic acid
	⊗ = heat
	<i>t</i> -Bu = <i>tert</i> -butyl
	PhCH <sub>3</sub> = toluene
20	Pd/C = palladium on activated charcoal
	TsCl = tosyl chloride
	TBSOTf = <i>tert</i> -butyldimethylsilyl trifluoromethane sulfonate
	TBS = <i>tert</i> -butyldimethylsilane
	MeI = methyl iodide
25	(BOC) <sub>2</sub> O = di- <i>tert</i> -butyl dicarbonate
	TEA = triethylamine
	<i>n</i> -BuLi = <i>n</i> -butyllithium
	rt = room temperature
	LC = liquid chromatography
30	Ts = tosyl
	Ph = phenyl
	EtOH = ethanol



	DCE = dichloroethane
	DMSO = dimethylsulfoxide
	Ra-Ni = Raney Nickel
	MS = molecular sieves
5	MS(ES) = Electro-Spray Mass Spectrometry
	mCPBA = m-chloroperoxybenzoic acid
	sat = saturated
	AcOH = acetic acid
	MeOH = methanol
10	Et <sub>2</sub> O = diethyl ether
	Ac = acetyl
	DEAD = diethyl azodicarboxylate
	h = hours
	Et = ethyl
15	WSDCC = water soluble dicarbonyl diimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	TBAF = tetrabutylammonium fluoride
	DBAD = di-terbutylazodicarboxylate
	DCC = Dicyclohexylcarbodiimide
20	Wilkinson's catalyst = RhCl(PPh <sub>3</sub> ) <sub>3</sub>
	ADDP = 1,1-[azodicarbonyl]dipiperidine
	DMA = dimethylacetamide
	DME = 1,2-dimethoxyethane
	BOP = benzotriazol-1-yloxytris(dimethylamino)-phosphonium
25	hexafluorophosphate
	HRMS = high resolution mass spectrometry
	TBME = MTBE = methyl <i>tert</i> -butyl ether (i.e., 2-methoxy-2-methyl-propane)

$\text{TiCl}_2\text{Cp}_2$  = bis(cyclopentadienyl)titanium dichloride

DPPA = diphenylphosphoryl azide

HMPA = hexamethylphosphoryl amide

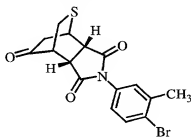
V% = volume percent

$\text{BH}_3 \cdot \text{DMS}$  = borane dimethylsulfate

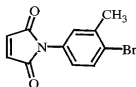
vvm = volume gas per volume liquid per minute

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10021873.121001

**Example 1****(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethanothiopyrano[3,4-c]pyrrole-1,3,8(2H,4H)-trione (1C)****5 A. 4-(tert-Butyldimethylsiloxy)-2H-thiopyran (1A)**

2,3-Dihydro-4H-thiopyran-4-one (1.50 g, 13.1 mmol, synthesized as described in Richards et al. *J. Org. Chem.* **46**, 4836-4842 (1981)) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (130 mL) and triethylamine (5.47 mL, 39.4 mmol) was added. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (3.62 mL, 15.8 mmol) was then added. After 10 minutes, the volatiles were removed *in vacuo* at 25°C. The resulting yellow oil was passed through a short column of SiO<sub>2</sub> eluting with 3% TEA in hexanes to yield 1.82 g (7.97 mmol, 61%) of compound **1A** as an orange oil.

**15 B. 1-[4-bromo-3-methylphenyl]-1H-pyrrole-2,5-dione (1B)**

4-Bromo-3-methylaniline (1.55 g, 8.33 mmol) and maleic anhydride (0.898 g, 9.16 mmol) were dissolved in acetic acid (10 mL) and heated at 115 °C for 12 h. The reaction was then cooled to 25°C and the acetic acid was removed *in vacuo*. The resulting residue was suspended in 5% K<sub>2</sub>CO<sub>3</sub> (100 mL), stirred for 25 minutes, filtered and rinsed with water. The material was then dried *in vacuo* to give 1.65 g (6.20 mmol, 74%) of compound **1B** as a light brown solid. HPLC: 100% at 2.96 min

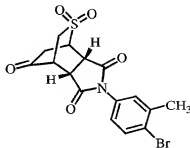
(retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm).

**C. (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethanothiopyrano[3,4-c]pyrrole-1,3,8(2H,4H)-trione (1C)**

- 5 Compound **1A** (0.313 g, 1.41 mmol) and compound **1B** (0.250 g, 0.940 mmol) were dissolved in toluene and heated to reflux for 5 h. The toluene was then removed by passing a stream of argon through the reaction flask. The residue was then purified by flash chromatography on SiO<sub>2</sub> eluting with 20% hexane in chloroform. This gave 0.168 g of the enol ether intermediate as a yellow solid. The enol ether intermediate was dissolved in dichloroethane (2.0 mL) and TFA (0.25 mL) was added. After 0.5 h, the reaction was quenched with saturated aqueous NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 mL). The organics were dried over anhydrous sodium sulfate and evaporated to give 0.079 g (0.21 mmol, 22%) of compound **1C** as a white solid. HPLC: 99% at 3.010 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 396.9 [M+ NH<sub>4</sub>]<sup>+</sup>.
- 10
- 15

**Example 2**

- 20 **(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethanothiopyrano[3,4-c]pyrrole-1,3,8(2H,4H)-trione 5,5-dioxide (2)**

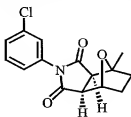


- Compound **1C** (0.040 g, 0.11 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) and cooled to 0°C. *m*-CPBA (60% purity, 0.061 g, 0.21 mmol) was added and the reaction was then warmed to 25°C. After 1 h, a 1:1 mixture of saturated NaHCO<sub>3</sub> and saturated sodium sulfite (20 mL) was added with vigorous stirring. After 15 minutes,
- 25

the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 30 mL) and the organics were dried over anhydrous sodium sulfate to yield 0.031 g (0.075 mmol, 71%) of compound **2** as a white solid. No purification was necessary. HPLC: 78% at 2.290 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  429.8  $[\text{M} + \text{NH}_4]^+$ .

### Example 3

#### (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3-Chlorophenyl)hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (3)

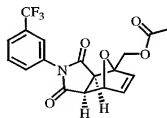
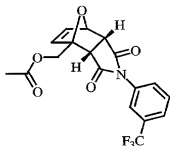


3-Chloroaniline (0.100 g, 0.787 mmol) and 3,6-endo-3-methylhexahydrophthalic anhydride (0.172 g, 0.945 mmol) were dissolved in AcOH (2.0 mL) and heated at 110°C for 11 h. The reaction was then cooled to 25°C, poured into cold saturated aq.  $\text{K}_2\text{CO}_3$  and stirred vigorously for 10 min. The solution was then filtered and rinsed with water. The resulting filtrate was dried *in vacuo* to give 0.118 g (0.404 mmol, 51%) of compound **3** as a white solid. No further purification was needed. HPLC: 99% at 2.510 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  292.32  $[\text{M} + \text{H}]^+$ .

**Example 4**

**(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[(Acetyloxy)methyl]-3a,4,7,7a-tetrahydro-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (4i and 4ii, respectively)**

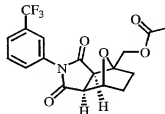
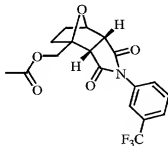
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- 2-Acetoxymethylfuran (0.599 mL, 4.78 mmol) and 1-[3-(trifluoromethyl)-phenyl]-1H-pyrrole-2,5-dione (0.500 g, 2.39 mmol, prepared as described in Example 1B) were dissolved in methylene chloride (3.0 mL) at 25°C. After 22 h, the volatiles were removed *in vacuo* and the resulting residue was purified by flash chromatography on SiO<sub>2</sub> eluting with 0-15% acetone in methylene chloride to give 0.438 g (1.15 mmol, 48%) of a yellow oil as a 2:1 mixture of compound 4i and compound 4ii, which was not separated. HPLC: 100% at 3.093 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 398.9 [M+ NH<sub>4</sub>]<sup>+</sup>.

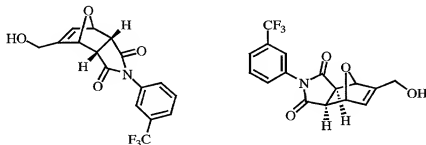
- Example 5**  
**(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[(Acetyloxy)methyl]-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (5i and 5ii, respectively)**

20



The 2:1 mixture of compounds **4i** and **4ii** (0.361 g, 0.948 mmol) was dissolved in ethyl acetate (25 mL) and Pd/C (10% Pd, 0.2 g) was added. Hydrogen was introduced via a balloon and the reaction was stirred at 25°C for 4 h, followed by filtration through Celite and rinsing with ethyl acetate. Concentration *in vacuo* gave 0.348 g (0.908 mmol, 96%) of a yellow oil that was determined to be a 2:1 mixture of compound **5i** and compound **5ii** (which was not separated). HPLC: 100% at 2.900 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  401.0  $[M+NH_4]^+$ .

**Example 6**  
**(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-3a,4,7,7a-Tetrahydro-5-(hydroxymethyl)-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (6i and 6ii, respectively)**

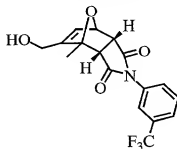


1-[3-(Trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (0.500 g, 2.39 mmol, prepared as described in Example 1B) and 3-furanmethanol (0.412 mL, 4.78 mmol) were dissolved in methylene chloride (3.0 mL) and stirred at 25°C for 20 h. The volatiles were then removed *in vacuo* and the resulting material purified by flash chromatography on SiO<sub>2</sub> eluting with chloroform/acetone to give 0.379 g (1.12 mmol, 47%) of compound **6i** and 0.220 g of compound **6ii**, both as white solids. Compound **6i**: HPLC: 100% at 2.197 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  338.0  $[M-H]^-$ . Compound **6ii**: HPLC: 100% at 2.477 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with

10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  338.0  $[M-H]^+$ .

#### Example 7

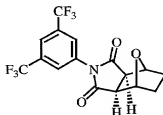
- 5 **(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-3a,4,7,7a-Tetrahydro-5-(hydroxymethyl)-4-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (7)**



- 2-Methyl-3-furanmethanol (0.537 g, 4.78 mmol) and 1-[3-(trifluoromethyl)-phenyl]-1H-pyrrole-2,5-dione (0.500 g, 2.39 mmol, prepared as described in Example 10 1B) were dissolved in dichloroethane (2.0 mL) and stirred at 25°C for 20 h. The reaction was then concentrated *in vacuo* and purified by flash chromatography in SiO<sub>2</sub> eluting with ethyl acetate/methylene chloride to give 0.317 g (0.897 mmol, 37.5%) of compound 7 as a white solid. No other possible isomer was isolated after chromatography. HPLC: 100% at 2.197 min (retention time) (YMC S5 ODS column 15 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  351.9  $[M-H]^+$ .

#### Example 8

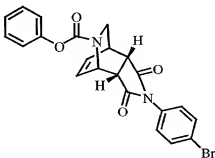
- 20 **(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-[3,5-Bis(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione (8)**



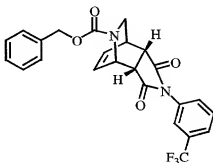
3,5-Bis(trifluoromethyl)aniline (0.017 g, 0.075 mmol) was dissolved in acetic acid (0.300 mL) and transferred to a 1.5 mL conical vial with a septa cap. Stock solutions of an additional 95 amines were prepared as described above. To each of



the above vials was added 0.40 mL (0.12 mmol) of a stock solution of exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride in acetic acid. The vials were then sealed and heated at 110°C for 11 h. Upon cooling to 25°C, the caps were removed from the vials and the acetic acid was removed *in vacuo*. To each vial was added 1 mL of 2:1 acetone/methylene chloride and the vials were heated at 40°C for 1 h. Once all products were in solution, they were transferred via robot to filter tubes with coarse frits pre-wetted with 0.2 mL of water. Nitrogen was blown through each tube until the volatile organics were removed. 1.5 mL of 10% aq. K<sub>2</sub>CO<sub>3</sub> was then added to each tube followed by vigorous shaking at 25°C for 15 min. The tubes were then drained, resealed and 1.0 mL of water was added to each tube followed by shaking. The tubes were drained again and washed with water a second time. The resulting residues in each tube were then dried *in vacuo* for 48 h. After drying, 1.0 mL of 20% TFA in methylene chloride was added to each tube and the racks were shaken for 30 min. The tubes were then drained into a 96-well plate with pre-tared custom micro-tubes present. Each tube was assayed for product purity (analytical LC) and identity (LC-MS). The tubes were then concentrated *in vacuo* and weighed for yields. The tube containing the reaction of 3,5-bistrifluoromethylaniline and exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride, yielded 0.022 g (0.058 mmol, 77%) of compound **8** as a white solid. HPLC: 94% at 4.03 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 434.2 [M+Na+MeOH]<sup>+</sup>. Of the remaining 95 additional reactions run, a total of 80 final compounds were obtained in >70% purity and >5 mg yield. Several samples needed further purification which was performed by short SiO<sub>2</sub> column eluting with methylene chloride/acetone. See Table 2 below.

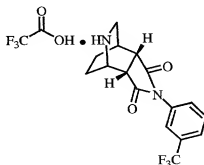
**Example 9****(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-(4-Bromophenyl)octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenyl ester (9)**

- 5 1-[4-Bromophenyl]-1H-pyrrole-2,5-dione (0.250 g, 0.992 mmol, prepared as described in Example 1B) and 1(2H)-pyridinecarboxylic acid phenylmethyl ester (0.299 g, 1.49 mmol, synthesized as described in Richard et al. *J. Org. Chem.* **46**, 4836-4842 (1981)) were dissolved in toluene and heated at 85°C for 1 h. Upon cooling to 25°C, the toluene was removed *in vacuo*. The resulting residue was
- 10 dissolved in a minimum amount of chloroform and the product was precipitated by addition of hexanes. After 1 h at 25°C, the product was filtered and rinsed with cold 20% hexanes in chloroform giving 0.243 g (0.536 mmol, 54%) of compound 9 as a white solid (single isomer). HPLC: 100% at 3.393 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes
- 15 containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 454.98 [M+H]<sup>+</sup>.

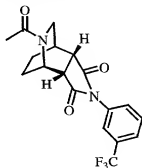
**Example 10****(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-(4-Bromophenyl)octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenylmethyl ester (10)**

1-[3-(Trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (3.78 g, 15.7 mmol, prepared as described in Example 1B) and 1(2H)-pyridinecarboxylic acid phenylmethyl ester (4.00 g, 18.8 mmol, synthesized as described in Richard et al. *J. Org. Chem.* **46**, 4836-4842 (1981)) were dissolved in toluene and heated at 80°C for 3 h. After cooling to 25°C, the toluene was removed *in vacuo* and the resulting residue was purified by flash chromatography on SiO<sub>2</sub> eluting with methanol/methylene chloride to give 3.20 g (7.01 mmol, 45%) of compound **10** as a yellow oil. HPLC: 95% at 3.510 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 457.2 [M+H]<sup>+</sup>.

**Example 11**  
**(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione trifluoroacetate (11)**

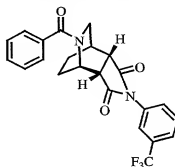


Compound **10** (3.20 g, 7.01 mmol) was dissolved in 100 mL of MeOH and 10% Pd/C Degussa catalyst (2.00 g, cat.) was added. Hydrogen was then introduced via a balloon. After 1 h, the reaction was filtered through Celite and rinsed with MeOH. The volatiles were removed *in vacuo* and the resulting crude material was purified by reverse phase preparative HPLC to yield 2.50 g (5.70 mmol, 81%) of compound **11** as the TFA salt (white solid). HPLC: 99% at 1.843 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 325.12 [M+H]<sup>+</sup>.

**Example 12****(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-5-Acetylhexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (12)**

- 5 Compound **11** (0.10 g, 0.23 mmol) was suspended in THF (5.0 mL) and TEA (0.097 mL, 0.46 mmol) was added resulting in a homogeneous solution. Acetyl chloride (0.033 mL, 0.46 mmol) was then added. After 2 h, the reaction was quenched with saturated aqueous NaHCO<sub>3</sub> and extracted with methylene chloride (3 x 15 mL). The crude material was purified by preparative TLC eluting with
- 10 chloroform/acetone to give 0.067 g (0.18 mmol, 79%) of compound **12** as a colorless oil. HPLC: 99% at 2.66 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 367.0 [M+H]<sup>+</sup>.

15

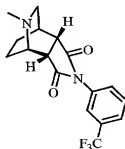
**Example 13****(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-5-Benzoylhexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (13)**

- 20 Compound **11** (0.10 g, 0.23 mmol) was suspended in THF (5.0 mL) and TEA (0.097 mL, 0.46 mmol) was added resulting in a homogeneous solution. Benzoyl chloride (0.053 mL, 0.46 mmol) was then added. After 2 h, the reaction was

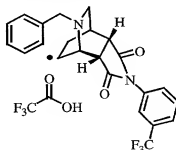
quenched with saturated aqueous  $\text{NaHCO}_3$  and extracted with methylene chloride (3 x 15 mL). The crude material was purified by reverse phase preparative HPLC to give 0.020 g (0.047 mmol, 20%) of compound **13** as a white foam. HPLC: 99% at 3.183 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  429.1  $[\text{M}+\text{H}]^+$ .

#### Example 14

(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-5-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (**14**)



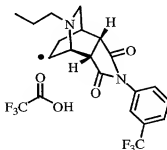
Compound **11** (0.10 g, 0.23 mmol) was suspended in THF (5.0 mL) and TEA (0.097 mL, 0.46 mmol) was added resulting in a homogeneous solution. Dimethyl sulfate (0.043 mL, 0.46 mmol) was added and the reaction was stirred at 25°C. After 14 h, the reaction was concentrated *in vacuo* and the crude material was purified by preparative TLC eluting with 10% MeOH in methylene chloride to give 0.030 g (0.088 mmol, 39%) of compound **14** as a white solid. HPLC: 100% at 1.797 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  339.21  $[\text{M}+\text{H}]^+$ .

**Example 15****(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-5-(phenylmethyl)-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione trifluoroacetate (15)**

- 5 Compound **11** (0.10 g, 0.23 mmol) was dissolved in DMF (5.0 mL) and  $K_2CO_3$  (0.063 g, 0.46 mmol) was added. Benzyl bromide (0.041 mL, 0.35 mmol) was then added. The reaction was stirred at 25°C for 1 h, filtered and concentrated *in vacuo*. The crude material was purified by reverse phase preparative HPLC to give
- 10 0.055 g (0.10 mmol, 43%) of compound **15** as a white solid. HPLC: 100% at 2.31 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  415.36  $[M+H]^+$ .

**Example 16**

- 15 **(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-5-propyl-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione trifluoroacetate (16)**

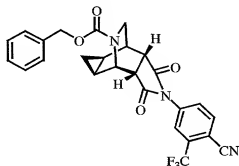


- 20 Compound **11** (0.10 g, 0.23 mmol) was dissolved in DMF (5.0 mL) and  $K_2CO_3$  (0.079 g, 0.57 mmol) was added, followed by 1-bromopropane (0.031 mL, 0.34 mmol). The reaction was stirred at 25°C for 6 h, then filtered and concentrated *in vacuo*. The crude material was purified by reverse phase preparative HPLC to give

0.070 g (0.15 mmol, 63%) of compound **16** as a white solid. HPLC: 100% at 1.907 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  340.22  $[M+H]^+$ .

5

**Example 17**  
**(3 $\alpha$ ,4 $\alpha$ ,4a $\beta$ ,5a $\beta$ ,6 $\alpha$ ,6a $\alpha$ )-2-[4-Cyano-3-(trifluoromethyl)phenyl]decahydro-1,3-dioxo-4,6-(iminomethano)cycloprop[flisoindole-7-carboxylic acid phenylmethyl ester (17)**



10

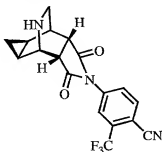
1-Methyl-3-nitro-1-nitrosoguanidine (2.5 g, 17 mmol) was added portionwise to a solution of 40% KOH/H<sub>2</sub>O (15 mL) and Et<sub>2</sub>O (25 mL) at 0°C. The ether layer turned yellow once addition was complete. After 30 min at 0°C, the ether layer was poured into a solution of (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7a $\alpha$ )-2-[4-cyano-3-(trifluoromethyl)phenyl]-

15

octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenylmethyl ester (0.500 g, 1.09 mmol, prepared as described in Example 10) and Pd(OAc)<sub>2</sub> (0.010 g) in THF (10 mL) at 0°C. The reaction was then warmed slowly to 25°C, stirred for 24 h and then filtered through Celite rinsing with THF. The crude material was then purified by flash chromatography on SiO<sub>2</sub> eluting with

20

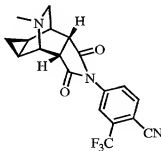
MeOH/CH<sub>2</sub>Cl<sub>2</sub> to give 0.34 g (0.69 mmol, 63%) of compound **17** as a white solid and a single isomer. HPLC: 100% at 3.61 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  496.25  $[M+H]^+$ .

**Example 18****(3 $\alpha$ ,4 $\alpha$ ,4a $\beta$ ,5a $\beta$ ,6 $\alpha$ ,6a $\alpha$ )-4-[Decahydro-1,3-dioxo-4,6-****(iminomethano)cycloprop[flisoindol-2-yl]-2-(trifluoromethyl)benzonitrile (18)**

5

Compound **17** (0.200 g, 0.404 mmol) was dissolved in MeOH (20 mL) and 5% Pd/C (0.200 g) was added. Hydrogen was then introduced via balloon. After 3 h, the reaction was filtered through Celite, rinsed with MeOH and the volatiles were removed *in vacuo* to yield 0.130 g (0.360 mmol, 89%) compound **18** as a white solid. HPLC: 100% at 1.80 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 362.09 [M+H]<sup>+</sup>.

15

**Example 19****(3 $\alpha$ ,4 $\alpha$ ,4a $\beta$ ,5a $\beta$ ,6 $\alpha$ ,6a $\alpha$ )-4-[Decahydro-7-methyl-1,3-dioxo-4,6-****(iminomethano)cycloprop[flisoindol-2-yl]-2-(trifluoromethyl)benzonitrile (19)**

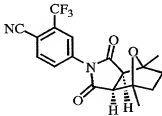
20

Compound **18** (0.100 g, 0.277 mmol) was dissolved in CH<sub>3</sub>CN (2.0 mL). TEA (0.19 mL, 1.4 mmol) and MeI (0.052 mL, 0.83 mmol) were then added and the reaction was stirred at 25°C for 14 h. The reaction was concentrated under reduced



pressure and the crude material was partitioned between  $\text{CH}_2\text{Cl}_2$ /water and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 15 mL). The combined organics were dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The crude material was purified by flash chromatography eluting with 3%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  to give 0.030 g (0.080 mmol, 29%) of compound **19** as a light yellow solid. HPLC: 100% at 1.720 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  376.11  $[\text{M}+\text{H}]^+$ .

10

**Example 20****(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (20B)****15 A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-epoxyisobenzofuran-1,3-dione (20A)**

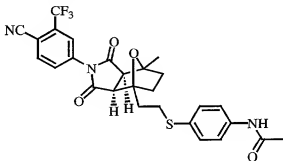
Freshly distilled dimethyl furan (1.60 mL, 15.3 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) and maleic anhydride (1.00 g, 10.2 mmol) was added. The reaction was stirred at 25°C for 16 h and was then concentrated *in vacuo* to give a yellow solid. This solid was dissolved in ethyl acetate (30 mL) and 10% Pd/C (0.200 g, cat.) was added. Hydrogen was then introduced via a balloon and the reaction stirred for 24 h. The reaction mixture was filtered through Celite rinsing with EtOAc followed by concentration *in vacuo* to give 1.69 g (8.61 mmol, 84%) of compound **20A** as a white solid. 2-Dimensional NOE experiments confirmed the structural assignment to be that of compound **20A**.

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (20B)**

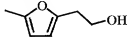
A solution of compound **20A** (603 mg, 3.21 mmol), 5-amino-2-cyanobenzotrifluoride (640 mg, 3.44 mmol) and TsOH (10 mg, cat.) in toluene (5 mL) was heated in a sealed tube for 2 days. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes gave 400 mg (1.10 mmol, 34%) of compound **20B** as a white solid. HPLC: 99% at 3.04 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI):  $m/z$  382.2  $[M+NH_4]^+$ .

**Example 21**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-N-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]thio]phenyl]acetamide (21E)**



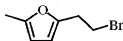
**A. 5-Methyl-2-furanethanol (21A)**



A solution of *n*-BuLi (83.0 mL, 133 mmol, 1.6 M in hexanes) was added to a stirred solution of 2-methylfuran (10.0 mL, 111 mmol) in THF (85 mL) at 0°C under inert atmosphere. The reaction mixture was stirred for 4 h at room temperature then cooled to 0°C. Ethylene oxide (8.30 mL, 166 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. After quenching with saturated aqueous  $NH_4Cl$ , the resulting layers were separated and the aqueous layer was extracted with  $Et_2O$  (2 X 250 mL). The combined organic layers were dried over  $Na_2SO_4$  and concentrated under reduced pressure. Distillation at

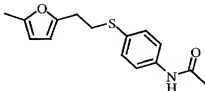
atmospheric pressure (170-185 °C) gave 10.1 g (80.3 mmol, 72%) of compound **21A** as a light yellow oil.

**B. 2-(2-Bromoethyl)-5-methylfuran (21B)**



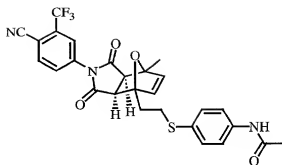
5 Ph3Br2 (3.68 g, 8.72 mmol) was added to a solution of compound **21A** (1.00 g, 7.93 mmol) in DMF (8 mL) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was added to H<sub>2</sub>O and extracted with EtOAc (3 X). The combined organic layers were washed with H<sub>2</sub>O (2 X), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 10% EtOAc/hexanes gave 0.507 g (2.68 mmol, 34%) of compound **21B**.

**C. N-[4-[[2-(5-Methyl-2-furanyl)ethyl]thio]phenyl]acetamide (21C)**



15 To a solution of 4-acetamidothiophenol (442 mg, 2.64 mmol) in THF (1 mL) at 0°C under inert atmosphere was added a solution of *n*-BuLi (2.00 mL, 3.17 mmol, 1.6 M in hexanes) in THF (1 mL). The reaction solution was stirred at room temperature for 10 min then a solution of compound **21B** (500 mg, 2.64 mmol) in THF (3 mL) was added. After the starting material was consumed (as determined by TLC), the reaction was quenched with H<sub>2</sub>O and the mixture was extracted with EtOAc (2X), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes gave 0.644 g (2.34 mmol, 88%) of compound **21C**. MS (ESI): *m/z* 276.09 [M+H]<sup>+</sup>.

**D. (3α,4β,7β,7α)-N-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]-1,2,3,3a,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]thio]phenyl]acetamide (21D)**



A solution of compound **21C** (195 mg, 0.708 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (377 mg, 1.416 mmol, prepared as described for Example 1B) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) was stirred at room temperature for two days. The reaction mixture was concentrated under reduced pressure to yield compound **21D** as determined by NMR analysis. Compound **21D** was used directly in the next step without purification.

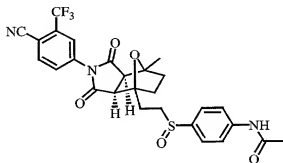
**E. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-N-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]-octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]thio]phenyl]acetamide (**21E**)**

A solution of crude compound **21D** (0.708 mmol) and 10% Pd/C (200 mg) in MeOH (20 mL) was stirred under a hydrogen atmosphere overnight. Purification by reverse phase HPLC [34.4 min (retention time) (YMC S5 ODS column 20 x 250 mm, 0-100% aqueous methanol over 30 minutes containing 0.1% TFA, 10 mL/min, monitoring at 220 nm)] followed by flash chromatography on silica gel eluting with 1% MeOH/ $\text{CH}_2\text{Cl}_2$  gave 29 mg (0.053 mmol, 7.5%) of compound **21E** as a yellow powder. HPLC: 99% at 3.44 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI):  $m/z$  544.01  $[\text{M}+\text{H}]^+$ .

**Example 22**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-N-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]sulfinyl]phenyl]acetamide (22)**

5



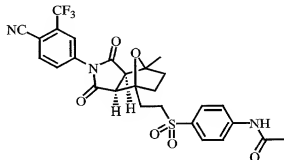
- m*CPBA (12 mg, 0.050 mmol) was added portionwise to a solution of crude compound **21E** (65 mg, 0.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) until the starting material was consumed. Purification by reverse phase HPLC [30.5 min (retention time) (YMC S5 ODS column 30 x 250 mm, 0-100% aqueous methanol over 30 minutes containing 0.1% TFA, 25 mL/min, monitoring at 220 nm)] gave 27.5 mg (0.0491 mmol, 41%) of compound **22** as a tan solid (~1:1 mixture of diastereomers). HPLC: 96% at 2.88 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm).
- MS (ESI): *m/z* 559.97 [M+H]<sup>+</sup>.

10024078.121901

**Example 23**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-N-[4-[[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]sulfonyl]phenyl]acetamide**  
**(23)**

5

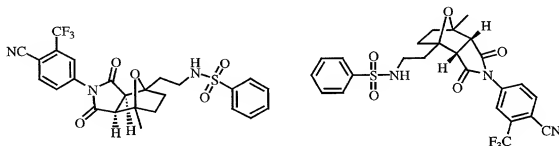
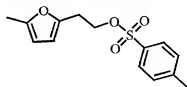


- m*CPBA (26 mg, 0.11 mmol) was added to a solution of compound **21E** (19 mg, 0.035 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) and the reaction was stirred at rt until starting material and the intermediate sulfoxide (compound **22**) were consumed as was
- 10 apparent by TLC. Purification by reverse phase preparative HPLC [53.3 min (retention time) (YMC S5 ODS column 30 x 250 mm, 0-70% aqueous methanol over 45 minutes containing 0.1% TFA, 25 mL/min, monitoring at 220 nm)] gave 8.0 mg (0.014 mmol, 40%) of compound **23** as a white solid. HPLC: 99% at 2.94 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over
- 15 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): *m/z* 575.95 [M+H]<sup>+</sup>.

**Example 24**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-N-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]benzenesulfonamide (24Ci and 24Cii, respectively)**

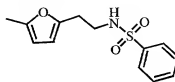
5

**A. 5-Methyl-2-furanethanol 4-methylbenzenesulfonate (24A)**

10

4-Methylbenzenesulfonyl chloride (907 mg, 4.76 mmol) was added to a solution of compound **21A** (500 mg, 3.96 mmol) in 6 mL of dry pyridine. The reaction was stirred at room temperature for 4 h and then quenched with ice. The reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic layers were washed with saturated aqueous sodium bicarbonate and water, dried and concentrated under reduced pressure to give 900 mg (81%) of compound **24A** as a yellow oil.

15

**B. N-[2-(5-Methyl-2-furanyl)ethyl]benzenesulfonamide (24B)**

20

Benzenesulfonamide (157 mg, 1.00 mmol) was added to a 10% aqueous solution of sodium hydroxide (0.40 mL, 1.0 mmol). A solution of compound **24A** (280 mg, 1.00 mmol) in acetone (1 mL) was then added. The reaction mixture was heated at 90°C for 8 h then cooled to room temperature. Ice was added and the

mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with water, dried and concentrated under reduced pressure. Purification by flash chromatography on silica gel, eluting with  $\text{CH}_2\text{Cl}_2$  gave 60 mg (0.23 mmol, 23%) of compound **24B** as yellow oil.

5

**C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-N-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]benzenesulfonamide (24Ci and 24Cii, respectively)**

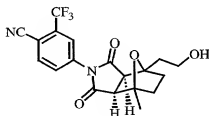
- 10 4-(2,5-Dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (129 mg, 0.485 mmol, prepared as described in Example 1B) was added to a solution of compound **24B** (60 mg, 0.23 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL). The reaction mixture was stirred at room temperature for 2 days, concentrated under reduced pressure and purified by flash chromatography on silica gel, eluting with 70% EtOAc/hexanes, to
- 15 give 20 mg (0.038 mmol, 16%) of the unsaturated Diels-Alder product. The unsaturated product (20 mg) was immediately dissolved in ethanol (2 mL) and 10% Pd/C (10 mg, cat.) was added. The solution was stirred at room temperature overnight under a hydrogen atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure. Purification by reverse phase preparative HPLC
- 20 gave 7.0 mg (0.013 mmol, 34%) of compound **24Ci** and 2.0 mg (0.0037 mmol, 10%) of compound **24Cii**. Compound **24Ci**: HPLC: 96% at 3.17 min (retention time) (YMC ODSA S5 C18 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.1% TFA, monitoring at 220 nm). MS (ES):  $m/z$ : 533.99  $[\text{M}+\text{H}]^+$ . Compound **24Cii**: HPLC: 99% at 38.95 min (retention time) (YMC ODS S5 20X250 mm, 10%-
- 25 90% aqueous methanol over 40 min gradient with 0.1% TFA, monitoring at 220 nm). MS (ES):  $m/z$  533.99  $[\text{M}+\text{H}]^+$ .

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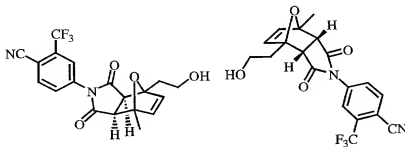


**Example 25**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (25B)**



**A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-4-[1,3,3a,4,7,7a-Hexahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (25Ai and 25Aii, respectively)**



- A solution of compound **21A** (252 mg, 2.00 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (798 mg, 3.00 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was stirred at room temperature for 2 days. The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 65% EtOAc/hexanes gave 217 mg of pure compound **25Ai**, 73 mg of pure compound **25Aii** and 310 mg of a mixture of both compound **25Ai** and **25Aii**.
- All three fractions were isolated as white solids with a total isolated yield of 600 mg (1.53 mmol, 76.5%). Compound **25Ai**: HPLC: 90% at 2.56 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). Compound **25Aii**: HPLC: 90% at 2.56 min (retention time) (YMC S5 ODS column 4.6 x 50 mm,

10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (25B)**

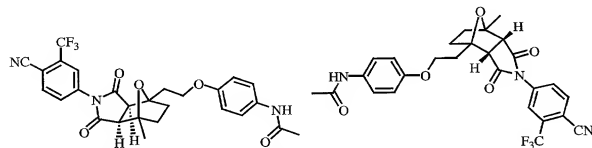
A solution of compound **25Ai** (0.20 g, 0.51 mmol) and 10% Pd/C (43 mg, cat.) in EtOH (12 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 0.20 g (0.51 mmol, 100%) of compound **25B** as a white solid. HPLC: 95% at 2.59 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 394.97 [M+H]<sup>+</sup>.

15

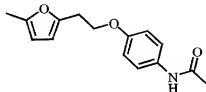
**Example 26**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-N-[4-[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]ethoxy]phenyl]acetamide (26Ci and 26Cii, respectively)**

20



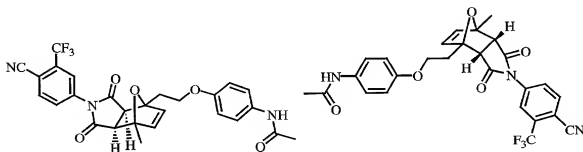
**A. 2-[4-[2-(5-Methyl-2-furanyl)ethoxy]phenyl]acetamide (26A)**



Triphenylphosphine (681 mg, 2.60 mmol) was added to a solution of compound **21A** (252 mg, 2.00 mmol) and 4-acetamidophenol (302 mg, 2.00 mmol) in

CH<sub>2</sub>Cl<sub>2</sub> (4 mL). THF (5 mL) was added to make the reaction mixture homogeneous and the mixture was then cooled to 0°C. DEAD (0.41 mL, 2.6 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight, then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 60% EtOAc/hexanes followed by reverse phase preparative HPLC gave 270 mg (1.04 mmol, 52%) of compound **26A** as a light brown solid. MS (ESI): m/z 260.09 [M+H]<sup>+</sup>.

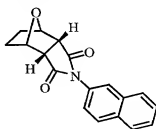
**B.** (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-N-[4-[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]-1,2,3,3a,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenyl]acetamide (**26Bi** and **26Bii**, respectively)



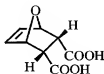
A solution of compound **26A** (40 mg, 0.15 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (88 mg, 0.31 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred at room temperature for 2 days. The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 75% EtOAc/hexanes gave 55 mg (0.105 mmol, 68%) of a 5:1 mixture of compounds **26Bi** and **26Bii** as a white solid, which was used directly in the next step. HPLC: 90% at 3.28 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**C.** (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-N-[4-[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenyl]acetamide (**26Ci** and **26Cii**, respectively)

A solution of a mixture of compounds **26Bi** and **26Bii** (55 mg, 0.105 mmol) and 10% Pd/C (12 mg, cat.) in EtOH (3 mL) was stirred under a hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 50 mg of crude product. Purification by flash chromatography on silica gel eluting with 70% EtOAc/hexanes gave 18 mg (0.034 mmol, 32%) of compound **26Ci** [HPLC: 96% at 3.33 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 528.01 [M+H]<sup>+</sup>; and 2.3 mg (0.0044 mmols, 4%) of an 85:15 mixture of **26Cii** and **26Ci** respectively as determined by <sup>1</sup>H NMR. HPLC: 90% at 3.35 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 528.12 [M+H]<sup>+</sup>.

**Example 27****(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (27D)**

20 A. (endo, endo)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid (27A)

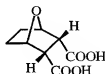


Compounds **27A**, **27B** and **27C** were synthesized in accordance with the approaches described in Sprague et al. *J. Med. Chem.* **28**, 1580-1590 (1985). A mixture of furan (100 mL, 1.38 mol) and maleic acid (160 g, 1.38 mol) in H<sub>2</sub>O (340 mL) was stirred at room temperature for 5 days. The mixture was placed in a separatory funnel and the aqueous layer was separated from the layer containing the

unreacted furan. The aqueous layer was treated with charcoal, filtered through Celite and placed in the refrigerator. The desired product crystallized from solution upon seeding, was filtered, washed with cold water and dried over  $P_2O_5$  to give 70 g (0.38 mol, 28%) of compound **27A** as a white solid.

5

**B. (endo, endo)-7-Oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid (27B)**



To a solution of compound **27A** (69.0 g, 0.375 mol) in EtOH (700 mL) was added 10% Pd/C (4.5 g, cat.) and the mixture was shaken under a hydrogen atmosphere at 55 psi until gas uptake ceased. The mixture was filtered through Celite and concentrated *in vacuo* to give 66.0 g (0.355 mol, 95%) of compound **27B** as a white solid.

15

**C. (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-4,7-epoxyisobenzofuran-1,3-dione (27C)**



A solution of compound **27B** (66.0 g, 355 mol) in acetyl chloride (300 mL) was refluxed for 1 h. The reaction solution was concentrated *in vacuo* and the resulting residue was recrystallized from benzene to give 49.2 g (0.292 mol, 82%) of compound **27C** as a white solid (>99% endo by  $^1H$  NMR).

20

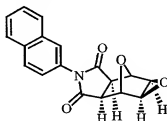
**D. (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (27D)**

Compound **27C** (45 mg, 0.30 mmol) was combined with 2-aminonaphthalene (47 mg, 0.33 mmol) in acetic acid (1 mL) and heated at 115°C overnight. After the

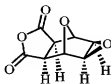
reaction was cooled to rt, a drop of water was added, and the resulting precipitate was filtered. The material was washed with methanol and dried to provide 65.7 mg (0.224 mmol, 74.7%) of compound **27D** as a white crystalline solid. HPLC: 99% at 2.68 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI):  $m/z$  294.0  $[M+H]^+$ .

**Example 28**

**(1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-Hexahydro-4-(2-naphthalenyl)-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione (28B)**



**A. (1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-Tetrahydro-2,6-epoxyoxireno[f]isobenzofuran-3,5(2aH,5aH)-dione (28A)**

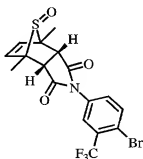


As described in Yur'ev et al. *J. Gen. Chem. U.S.S.R. (Engl. Transl.)* **31**, 772-775 (1961), a solution of exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride (5.00 g, 30.1 mmol), formic acid (10 mL) and hydrogen peroxide (6 mL) was stirred at room temperature. After 30 min, the reaction was placed in an ice bath (it became exothermic along with gas evolution) and was allowed to warm to room temperature slowly. After stirring overnight, the resulting precipitate was collected by filtration and washed with glacial acetic acid and dried to yield 3.02 g of a white powder. The crude solid was boiled in acetyl chloride (100 mL) for 10 hours and the mixture was concentrated to ~20 mL under reduced pressure. The resulting precipitate was filtered, washed with dioxanes and dried to give 2.37 g (13.0 mmol, 43%) of compound **28A** as a white powder.

**B. (1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-Hexahydro-4-(2-naphthalenyl)-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione (28B)**

- 5 Compound **28A** (100 mg, 0.520 mmol) was combined with 2-aminonaphthalene (62.1 mg, 0.434 mmol) in acetic acid (2 mL) and heated at 115°C overnight. After the reaction was allowed to cool to rt, water was added, and the resulting precipitate was filtered. The material was washed sequentially with aqueous K<sub>2</sub>CO<sub>3</sub> and water and then dried in a vacuum oven to provide 113.7 mg (0.371 mmol, 10 85.5%) of compound **28B** as an off-white crystalline solid. HPLC: 99% at 1.76 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 308.0 [M+H]<sup>+</sup>.

- 15 **Example 29**  
**(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-[4-Bromo-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-dimethyl-4,7-epithio-1H-isoindole-1,3(2H)-dione 8-oxide (29)**



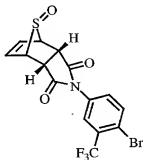
- 20 2,5-Dimethylthiophene (0.048 mL, 0.42 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (0.290 g, 0.625 mmol, prepared as described for Example 1B) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) and cooled to -20 °C. BF<sub>3</sub>•Et<sub>2</sub>O (0.412 mL, 3.36 mmol) was added slowly followed by addition of *m*CPBA (~50%, 0.29 g, 0.84 mmol). After 2 h at -20 °C, the reaction mixture was poured into 25 saturated aq. NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL) and the organics dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by flash chromatography on SiO<sub>2</sub> eluting with 5%-10%-20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub> to give 0.119 g (0.265 mmol, 63%)

of compound **29** as a white solid. HPLC: 91% at 3.303 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI):  $m/z$  480.2  $[M+H]^+$ .

5

### Example 30

#### (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-[4-Bromo-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-epithio-1H-isoindole-1,3(2H)-dione 8-oxide (30)



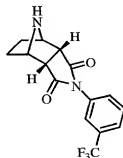
10

Thiophene (0.375 mL, 4.69 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (0.100 g, 0.313 mmol, prepared as described for Example 1B) were dissolved in  $CH_2Cl_2$  (50 mL), *m*CPBA (~50%, 1.62 g, 4.69 mmol) was added and the resulting mixture was stirred at 25°C for 3 h. Triphenylphosphine (2.0 g) was then added. After 15 min, the volatiles were removed *in vacuo* and the resulting residue was dissolved in  $CH_2Cl_2$  (200 mL) and washed with saturated aq.  $NaHCO_3$  (3 x 50 mL) and dried over  $Na_2SO_4$ . The crude material was then purified by flash chromatography on  $SiO_2$  eluting with 1% - 3% - 5% methanol in  $CH_2Cl_2$  to give 0.059 g (0.14 mmol, 45%) compound **30** as a white powder. NMR and LC

analysis showed a single diastereomer. HPLC: 100% at 3.437 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI):  $m/z$  443.2  $[M+H]^+$ .

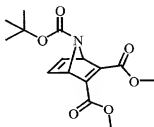
25



**Example 31****(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-imino-1H-isoindole-1,3(2H)-dione (31D)**

5

- A. **7-Azabicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylic acid 2,3-dimethyl 7-(1,1-dimethylethyl) ester (31A)**

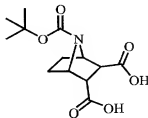


10

Freshly distilled acetylenedicarboxylic acid dimethyl ester (6.7 mL, 54 mmol) and *N*-(*tert*-butoxycarbonyl)-1H-pyrrole (9.0 mL, 54 mmol) were combined and heated at 120°C for 3 h. Purification by flash chromatography on SiO<sub>2</sub> eluting with EtOAc/CH<sub>2</sub>Cl<sub>2</sub> gave 8.3 g (27 mmol, 50%) of compound **31A** as a yellow solid.

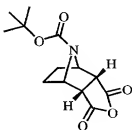
15

- B. **(exo,endo)-7-Azabicyclo[2.2.1]hept-2,5-diene-2,3,7-tricarboxylic acid 7-(1,1-dimethylethyl) ester (31B)**



Compound **31A** (1.0 g, 3.5 mmol) was dissolved in MeOH (2.0 mL) and aq. KOH (1 g in 5 mL H<sub>2</sub>O) was added. The reaction was heated at 50°C for 1 h. The reaction was then cooled to 25°C and 10% Pd/C (0.5 g, cat.) was added and the mixture was placed in a Parr apparatus for 14 h at 25°C. The reaction was then  
 5 filtered through Celite rinsing with water. The aqueous solution was acidified to pH 2 by addition of 1 N HCl and then extracted with EtOAc (2 x 100 mL). Concentration of the organics gave the compound **31B** as a pale yellow solid.

**C. (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-1,3-dioxo-4,7-iminoisobenzofuran-8-carboxylic acid 1,1-dimethylethyl ester (31C)**



Crude compound, **31B**, was heated to 120°C *in vacuo* in a sublimation chamber, resulting in sublimation of 0.051 g (0.19 mmol, 5.4%) of compound **31C** as a white solid, which was collected directly and used in the next step without further  
 15 purification.

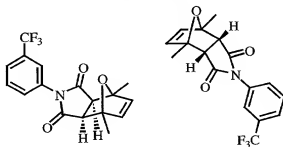
**D. (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-imino-1H-isoindole-1,3(2H)-dione (31D)**

Compound **31C** (0.050 g, 0.19 mmol) and the 1-amino-3-(trifluoromethyl)benzene (0.030 g, 0.19 mmol) were dissolved in AcOH (2.5 mL) and heated at 115°C for 4.5 h. The reaction was quenched by addition of saturated aqueous NaHCO<sub>3</sub> and the mixture was extracted with methylene chloride (3 x 15  
 25 mL). The crude material was purified by reverse phase preparative HPLC to give 0.030 g (0.097 mmol, 51%) of compound **31D** as a white solid. HPLC: 99% at 2.33 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol

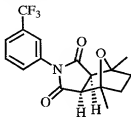
over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).  
MS (ESI):  $m/z$  311.15  $[M+H]^+$ .

**Example 32**

- 5 **(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-3a,4,7,7a-Tetrahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (32i and 32ii, respectively)**



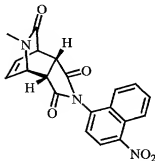
- Freshly distilled 2,5-dimethylfuran (0.32 mL, 2.6 mmol) was dissolved in  
10  $\text{CH}_2\text{Cl}_2$  (2.0 mL) and 1-[3-(trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (0.5 g, 2.5 mmol, prepared as described in Example 1B) was added. The reaction was stirred at 25°C for 16 h and was then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 0.5%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  gave 250 mg (0.741 mmol, 30%) of compound **32i**, and 50 mg (0.15 mmol, 6%) of compound **32ii**  
15 as white solids. Compound **32i**: HPLC: 98% at 3.080 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  338.30  $[M+H]^+$ . Compound **32ii**: HPLC: 92% at 3.047 min (retention time) (YMC S5 ODS  
20 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES):  $m/z$ : 338.15  $[M+H]^+$ .

**Example 33****(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (33)**

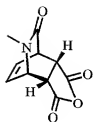
- 5 Compound **32i** (0.080 g, 0.24 mmol) was dissolved in EtOAc (2 mL) and EtOH (1 mL) and 10% Pd/C (0.050 g, cat.) was added. Hydrogen was then introduced by a balloon and the reaction was stirred for 24 h. The mixture was filtered through Celite, rinsed with EtOAc and concentrated *in vacuo* to give 0.075 g (0.22 mmol, 93%) of compound **33** as a white solid. No further purification was
- 10 needed. HPLC: 90% at 3.233 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 340.40 [M+H]<sup>+</sup>.

**Example 34**

- 15 **(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Tetrahydro-5-methyl-2-(4-nitro-1-naphthalenyl)-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione (34B)**



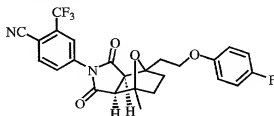
- A. **4,5,7,7a-Tetrahydro-5-methyl-4,7-ethenofuro[3,4-c]pyridine-1,3,6(3aH)-trione (34A)**



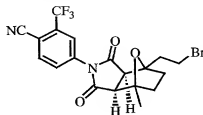
Compound **34A** was synthesized by a modification of the methods described by Tomisawa et al. *Heterocycles* **6**, 1765-1766 (1977) & *Tetrahedron Lett.* **29**, 2465-2468 (1969). Maleic anhydride (2.00 g, 20.4 mmol) and 1-methyl-2-pyridone (2.22 g, 20.4 mmol) were suspended in 30 mL of anhydrous toluene. The reaction vessel was fitted with a Dean Stark trap and refluxed for 48 hours. The dark colored solution was allowed to cool to rt and then the volatiles were removed *in vacuo*. The resulting brown paste (4 g) was dissolved in 10 mL of boiling toluene and the hot solution was filtered under a nitrogen flow to remove particulates. On standing at 25°C the desired product precipitated from solution. The solid was isolated by filtration and washed with cold toluene to give 1.0 g (4.8 mmol, 24%) of compound **34A**, which was used without further purification.

**B. (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Tetrahydro-5-methyl-2-(4-nitro-1-naphthalenyl)-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione (**34B**)**

1-Amino-4-nitronaphthalene (0.094 g, 0.50 mmol) and compound **34A** (0.130 g, 0.627 mmol) were dissolved in AcOH (2.0 mL) and heated at 110°C for 11 h. The reaction was then cooled to 25°C and poured into cold saturated aqueous K<sub>2</sub>CO<sub>3</sub> and stirred vigorously for 10 min. The solution was filtered and rinsed with water. The resulting filtrate was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 4:6 EtOAc/hexanes to give 0.172 g (0.456 mmol, 91%) of compound **34B** as a white solid. HPLC: 92% at 2.472 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 378.29 [M+H]<sup>+</sup>.

**Example 35****(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-(2-(4-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (35)**

- 5 DEAD (0.060 mL, 0.38 mmol) was added to a solution of triphenylphosphine (100 mg, 0.380 mmol) in THF (1.3 mL) at room temperature under an inert atmosphere. After stirring for 10 min, 4-fluorophenol (43 mg, 0.380 mmol) was added in one portion. The reaction mixture was stirred for 5 min, compound **25B** (100 mg, 0.254 mmol) was added and stirring was continued for 3.5 h. Purification
- 10 by flash chromatography on silica gel eluting with 50% EtOAc/hexanes followed by reverse phase preparative HPLC [11.93 min (retention time) (YMC S5 ODS column 20 x 100 mm, 0-100% aqueous methanol over 10 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 72 mg (58%) of compound **35** as a solid. HPLC: 99% at 3.74 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-
- 15 90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI):  $m/z$  487.1 [M-H].

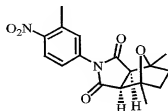
**Example 36****(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-(2-Bromoethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (36)**

- A solution of **25B** (495 mg, 1.26 mmol) and pyridine (100  $\mu$ L, 1.26 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added to a solution of  $\text{Ph}_3\text{PBr}_2$  (636 mg, 1.51 mmol) in  $\text{CH}_2\text{Cl}_2$
- 25 (2 mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hr, then

the solvent was removed under reduced pressure. The resulting residue was washed 2X with 10 mL portions of EtOAc-hexane (6:4) and the combined washings were purified by flash chromatography on silica gel eluting with 60% EtOAc/hexane to give 390 mg (0.853 mmol, 67.7%) of compound **36** as a white solid. HPLC: 99% at 3.51 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI):  $m/z$  456.7  $[M-H]^-$ .

### Example 37

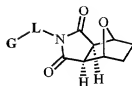
#### (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-(3-methyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (**37**)



A combination of 4-nitro-3-methylaniline (0.050 g, 0.33 mmol), compound **20A** (0.083 g, 0.43 mmol), TEA (0.2 mL),  $MgSO_4$  (0.075 g) and toluene (0.8 mL) were combined in a sealed tube and the mixture was heated at 120°C for 14 h. After cooling to 25°C, the reaction was filtered, rinsed with  $CH_2Cl_2$  and concentrated under reduced pressure. The crude product was purified by preparative TLC on  $SiO_2$  eluting with  $CH_2Cl_2$  to give 0.075 g (0.23 mmol, 69%) of compound **37** as a pale yellow solid. HPLC: 100% at 2.733 min (retention time) (YMC S5 ODS column, 4.6 X 50 mm; 10-90% MeOH/ $H_2O$  gradient, + 0.1% TFA; 4 mL/min, 220 nm detection). MS (ES):  $m/z$  348.2  $[M+NH_4]^+$ .

### Examples 38 to 121

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 38 to 121 have the following structure (L is a bond):











- 5 where G, the compound name, retention time, molecular mass, and the procedure employed, are set forth in **Table 2**. The chromatography techniques used to determine the compound retention times of **Table 2** are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. The molecular mass of the
- 10 compounds listed in **Table 2**, where provided, were determined by MS (ES) by the formula m/z.





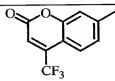
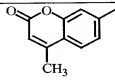


**Table 2**

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
38		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2-Fluorenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.72 LCMS/ 332.20 [M+H] <sup>+</sup>	8
39		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-[3-Chloro-4-(4-morpholinyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.20 LCMS/ 363.20 [M+H] <sup>+</sup>	8
40		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2,3-Dihydro-1H-inden-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.26 LCMS/ 284.22 [M+H] <sup>+</sup>	8











Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
41		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Bromo-1-naphthalenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.73 LCMS/ 404.11 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
42		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Chloro-1-naphthalenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.63 LCMS/ 328.14 [M+H] <sup>+</sup>	8
43		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(5-Amino-1-naphthalenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	1.64 LCMS/	8
44		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(7-hydroxy-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.54 LCMS/ 308.23 [M-H] <sup>-</sup>	8
45		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.117 LCMS/ 404.11 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
46		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(1H-indol-5-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.39 LCMS/ 283.23 [M+H] <sup>+</sup>	8
47		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(1H-indazol-6-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.35 LCMS/ 282.23 [M-H] <sup>-</sup>	8
48		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(1,3-Benzodioxol-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.47 LCMS/ 288.20 [M+H] <sup>+</sup>	8

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Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
49		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-[4-Amino-3-(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.71 LCMS/ 327.20 [M+H] <sup>+</sup>	8
50		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3-Chloro-4-iodophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.70 LCMS/ 435.2 [M+CH <sub>3</sub> OH] <sup>+</sup>	8
51		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(8-quinolinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.28 LCMS/ 295.22 [M+H] <sup>+</sup>	8
52		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.55 LCMS/ 302.23 [M+H] <sup>+</sup>	8
53		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-[2-oxo-4-(trifluoromethyl)-2H-1-benzopyran-7-yl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.38 LCMS/ 412.17 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
54		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(4-methyl-2-oxo-2H-1-benzopyran-7-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.74 LCMS/ 326.20 [M+H] <sup>+</sup>	8
55		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2,5-Dimethoxy-4-nitrophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.70 LCMS/ 349.23 [M+H] <sup>+</sup>	8
56		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2,3,5,6-Tetrafluoro-4-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile	2.97 LCMS	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
57		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(2,4,5-trifluorophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.90 LCMS	8
58		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(2,4,5-trichlorophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.64 LCMS/ 346.39 [M] <sup>+</sup>	8
59		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2-Amino-4,5-dichlorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.23 LCMS	8
60		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3,4-Difluorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.91 LCMS/ 280.23 [M+H] <sup>+</sup>	8
61		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-1-Acetyl-2,3-dihydro-6-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1H-indole	2.43 LCMS/ 359.26 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
62		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3-Chloro-4-fluorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.21 LCMS/ 328.14 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
63		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3,4-Dichlorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.54 LCMS/ 311.79 [M-H] <sup>-</sup>	8
64		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(3,4,5-trichlorophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	4.05 LCMS/ 378.10 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
65		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3-Chloro-4-methoxyphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.99 LCMS/ 308.11 [M+H] <sup>+</sup>	8
66		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3-Chloro-4-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.39 LCMS/ 292.20 [M+H] <sup>+</sup>	8
67		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(2-methyl-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.28 LCMS/ 308.23 [M+H] <sup>+</sup>	8
68		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Chloro-3-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.40 LCMS/ 292.20 [M+H] <sup>+</sup>	8
69		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3,4-Dimethylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.11 LCMS/ 272.23 [M+H] <sup>+</sup>	8
70		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-[4-Bromo-3-(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.76 LCMS/ 421.98 [M+CH3OH+H] <sup>+</sup>	8
71		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Bromo-3-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.50 LCMS/ 336.05 [M+H] <sup>+</sup>	8
72		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Fluoro-3-nitrophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.80 LCMS/ 305.25 [M-H] <sup>-</sup>	8


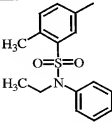
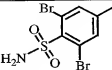


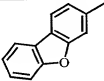
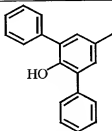

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
73		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-[4-Fluoro-3-(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.45 LCMS/ 362.26 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
74		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-(4-Chloro-3-nitrophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.19 LCMS/ 322.86 [M] <sup>+</sup>	8
75		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-[4-Chloro-3-(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.68 LCMS/ 345.83 [M] <sup>+</sup>	8
76		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-(4-Chloro-2-methoxy-5-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.31 LCMS/ 322.20 [M+H] <sup>+</sup>	8
77		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-(4-Amino-3-nitrophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.34 LCMS/ 302.27 [M-H] <sup>-</sup>	8
78		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-Hexahydro-2-(4-methyl-3-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.02 LCMS/ 335.20 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
79		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-(3,4-Dimethoxyphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.35 LCMS/ 304.25 [M+H] <sup>+</sup>	8
80		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-Hexahydro-2-(3-hydroxy-4-methoxyphenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	0.98 LCMS/ 321.19 [M+CH <sub>3</sub> OH] <sup>+</sup>	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
81		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(4-methyl-5-nitro-2-pyridinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	0.54 LCMS/ 304.20 [M+H] <sup>+</sup>	8
82		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-Chloro-4-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)- $\alpha$ -phenylbenzeneacetonitrile	3.67 LCMS/ 423.8 [M+CH <sub>3</sub> OH] <sup>+</sup>	8
83		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(2-methoxy-3-dibenzofuranyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.66 LCMS/ 364.25 [M+H] <sup>+</sup>	8
84		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(2,3,4-trifluorophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.06 LCMS/ 298.14 [M+H] <sup>+</sup>	8
85		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2,3-Dihydro-2-methyl-1,3-dioxo-1H-isoindol-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.70 LCMS/ 359.22 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
86		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Bromo-2,3,5,6-tetrafluorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.72 LCMS/ 426.07 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
87		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(2-hydroxy-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.52 LCMS/ 308.26 [M-H] <sup>-</sup>	8
88		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-[2,5-Dichloro-4-(1H-pyrrol-1-yl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.70 LCMS/ 376.64 [M-H] <sup>-</sup>	8

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Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
89		(3α,4β,7β,7α)-Hexahydro-2-[4-(methoxymethyl)-2-oxo-2H-1-benzopyran-7-yl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.79 LCMS/ 356.26 [M+H] <sup>+</sup>	8
90		(3α,4β,7β,7α)-2-(6-Benzothiazolyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.46 LCMS/ 301.19 [M+H] <sup>+</sup>	8
91		(3α,4β,7β,7α)-2-Methoxy-4-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzoic acid methyl ester	2.75 LCMS/ 332.25 [M+H] <sup>+</sup>	8
92		(3α,4β,7β,7α)-2-Methyl-5-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile	2.80 LCMS/ 315.26 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
93		(3α,4β,7β,7α)-Hexahydro-2-(2-oxo-2H-1-benzopyran-6-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.45 LCMS/ 312.20 [M+H] <sup>+</sup>	8
94		(3α,4β,7β,7α)-Hexahydro-2-(2,3,5,6-tetramethyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.59 LCMS/ 377.25 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
95		(3α,4β,7β,7α)-Hexahydro-2-(2,4,5-trimethylphenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.33 LCMS/ 286.30 [M+H] <sup>+</sup>	8
96		(3α,4β,7β,7α)-2-(4-Fluoro-3-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.00 LCMS/ 276.23 [M+H] <sup>+</sup>	8


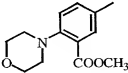





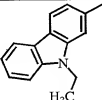
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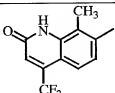
Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
97		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(3-methoxy-4-methylphenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.05 LCMS/ 288.23 [M+H] <sup>+</sup>	8
98		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-N-Ethyl-2-methyl-5-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-N-phenylbenzenesulfonamide	3.56 LCMS/ 441.26 [M+H] <sup>+</sup>	8
99		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2,6-Dibromo-4-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzenesulfonamide	2.25 LCMS	8
100		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2,4-Dimethyl-6-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-pyridinecarbonitrile	2.75 LCMS/ 298.23 [M+H] <sup>+</sup>	8
101		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2,3-Dimethyl-1H-indol-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.00 LCMS/ 311.26 [M+H] <sup>+</sup>	8
102		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(3-Dibenzofuranyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.72 LCMS/ 366.23 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
103		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(2'-hydroxy[1,1':3',1''-terphenyl]-5'-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.70 LCMS/ 412.23 [M+H] <sup>+</sup>	8
104		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(5,6,7,8-tetrahydro-3-hydroxy-2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.24 LCMS/ 312.32 [M+H] <sup>+</sup>	8



Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
105		(3α,4β,7β,7α)-2-(2,3-Dihydro-1H-indol-6-yl)hexahydro-4,7-epoxy-1H-isindole-1,3(2H)-dione	2.42 LCMS/ 285.29 [M+H] <sup>+</sup>	8
106		(3α,4β,7β,7α)-2-(1,3-Dihydro-2,2-dioxidobenzo[c]thiophen-5-yl)hexahydro-4,7-epoxy-1H-isindole-1,3(2H)-dione	1.99 LCMS/ 366.26 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
107		(3α,4β,7β,7α)-Hexahydro-2-(2-hydroxy-4,5-dimethylphenyl)-4,7-epoxy-1H-isindole-1,3(2H)-dione	2.78 LCMS/ 286.32 [M-H] <sup>-</sup>	8
108		(3α,4β,7β,7α)-2-(2,3-Dihydro-2,2,3,3-tetrafluoro-1,4-benzodioxin-6-yl)hexahydro-4,7-epoxy-1H-isindole-1,3(2H)-dione	3.82 LCMS/ 406.19 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
109		(3α,4β,7β,7α)-Hexahydro-2-(1H-indazol-5-yl)-4,7-epoxy-1H-isindole-1,3(2H)-dione	2.13 LCMS/ 284.23 [M+H] <sup>+</sup>	8
110		(3α,4β,7β,7α)-2-(4-Amino-2,3,5,6-tetrafluorophenyl)-hexahydro-4,7-epoxy-1H-isindole-1,3(2H)-dione	2.60 LCMS/ 363.22 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
111		(3α,4β,7β,7α)-2-(4-Bromo-3-chlorophenyl)hexahydro-4,7-epoxy-1H-isindole-1,3(2H)-dione	3.64 LCMS/ 389.64 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
112		(3α,4β,7β,7α)-Hexahydro-2-(5-hydroxy-1-naphthalenyl)-4,7-epoxy-1H-isindole-1,3(2H)-dione	2.48 LCMS/ 308.27 [M-H] <sup>-</sup>	8

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Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
113		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.28 LCMS/ 337.16 [M+H] <sup>+</sup>	8
114		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Morpholinyl)-5-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzoic acid methyl ester	2.72 LCMS/ 387.17 [M+H] <sup>+</sup>	8
115		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-Fluoro-5-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile	2.69 LCMS/ 319.26 [M+CH <sub>3</sub> OH+H] <sup>+</sup>	8
116		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Bromophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	5.80 LCMS/ 393.0 [M+H] <sup>+</sup>	8
117		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	6.92 LCMS/ 333.7 [M+H] <sup>+</sup>	8
118		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.27 LCMS/ 312.2 [M+H] <sup>+</sup>	8
119		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-2-(4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.88 LCMS/ 343.2 [M+H] <sup>+</sup>	8
120		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(9-Ethyl-9H-carbazol-3-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.73 LCMS/ 360.1 [M+H] <sup>+</sup>	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
121		(3α,4β,7β,7α)-2-[1,2-Dihydro-8-methyl-2-oxo-4-(trifluoromethyl)-7-quinolinyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.11 LCMS/ 393.0 [M+H] <sup>+</sup>	8

### Examples 122 to 164

Further compounds of the present invention were prepared by procedures analogous to those described above. **Table 3** provides the compound name and

5 structure, retention time, as well as the Example number of the procedure on which the preparation of **Table 3** was based, for the compounds of Examples 122 to 164.

The chromatography techniques used to determine the compound retention times of **Table 3** are as follows:

10 **LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

**LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm

**Table 3**

<b>Ex. No.</b>	<b>Compound Structure</b>	<b>Compound Name</b>	<b>Retention Time Min/ Molecular Mass</b>	<b>Pro. of Ex.</b>
122		(3α,4α,7α,7α)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.66 LCMS	27
123		(3α,4α,7α,7α)-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.76 LCMS	27
124		(3α,4β,7β,7α)-2-(4-Bromo-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	6.36 LCMS	8
125		(3α,4β,7β,7α)-2-(4-Bromophenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	5.72 LCMS	8
126		(3α,4β,7β,7α)-3a,4,7,7a-Tetrahydro-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	5.92 LCMS	8

Ex. No.	Compound Structure	Compound Name	Retention Time Min/ Molecular Mass	Pro. of Ex.
127		(3α,4β,7β,7α)-2-(9-Ethyl-9H-carbazol-3-yl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.73 LCMS	8
128		(3α,4β,7β,7α)-2-[4-Fluoro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.40 LCMS	8
129		(3α,4β,7β,7α)-2-[1,2-Dihydro-8-methyl-2-oxo-4-(trifluoromethyl)-7-quinolyl]-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.14 LCMS	8
130		(3α,4α,7α,7α)-4-[(Acetyloxy)methyl]-2-(4-bromo-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.95 LC	4
131		(3α,4β,7β,7α)-4-[(Acetyloxy)methyl]-2-(4-bromo-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.97 LCMS	5

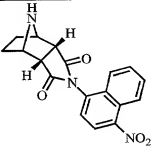
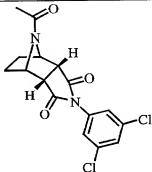
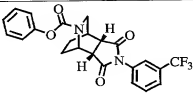
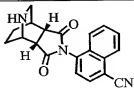
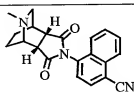
Ex. No.	Compound Structure	Compound Name	Retention Time Min./Molecular Mass	Pro. of Ex.
132		(3α,4β,7β,7α)-Hexahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.08 LC	20
133		(3α,4β,7β,7α)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-naphthalenecarbonitrile	3.00 LC	20
134		(3α,4β,7β,7α)-(Benzo[b]thiophen-3-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.61 LC	20
135		(3α,4β,7β,7α)-Hexahydro-4,7-dimethyl-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.21 LC	20
136		(3α,4β,7β,7α)-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-naphthalenecarbonitrile	2.94 LC	32
137		(3α,4α,7α,7α)-Hexahydro-4-methyl-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.88 LC	3

Ex. No.	Compound Structure	Compound Name	Retention Time Min./Molecular Mass	Pro. of Ex.
138		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-(4-Bromo-3-methylphenyl)hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.11 LC	3
139		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-Hexahydro-4-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.90 LC	3
140		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-(3,5-Dichlorophenyl)hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.31 LC	3
141		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-(3-Chloro-4-fluorophenyl)-hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.72 LC	3
142		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-Methoxy-4-(octahydro-1,3-dioxo-4-methyl-4,7-epoxy-2H-isoindol-2-yl)-1-naphthalenecarbonitrile	2.72 LC	3
143		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-Hexahydro-4-methyl-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.10 LC	3

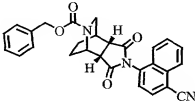
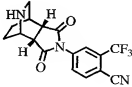
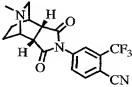
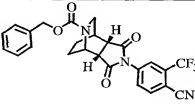
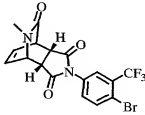
Ex. No.	Compound Structure	Compound Name	Retention Time Min/ Molecular Mass	Pro. of Ex.
144		(3α,4β,7β,7α)-Hexahydro-2-[4-(1H-imidazol-1-yl)phenyl]-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	1.16 LC	3
145		(3α,4β,7β,7α)-2-[3-Chloro-4-(2-thiazolyl)phenyl]hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.81 LC	3
146		(3α,4α,7α,7α)-2-(3,5-Dichlorophenyl)hexahydro-4,7-imino-1H-isoindole-1,3(2H)-dione	2.72 LC	31
147		(3α,4α,7α,7α)-2-(4-Bromo-1-naphthalenyl)hexahydro-4,7-imino-1H-isoindole-1,3(2H)-dione	2.95 LC	31
148		(3α,4α,7α,7α)-2-(4-Bromo-3-methylphenyl)hexahydro-4,7-imino-1H-isoindole-1,3(2H)-dione	2.65 LC	31

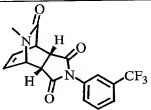
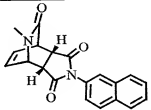
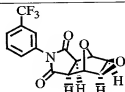
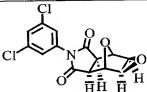
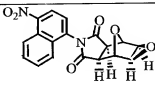
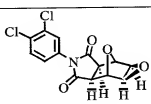
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Ex. No.	Compound Structure	Compound Name	Retention Time Min./Molecular Mass	Pro. of Ex.
149		(3α,4α,7α,7α)-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,7-imino-1H-isoindole-1,3(2H)-dione	2.49 LC	31
150		(3α,4α,7α,7α)-8-Acetyl-2-(3,5-dichlorophenyl)hexahydro-4,7-imino-1H-isoindole-1,3(2H)-dione	3.53 LC	31, 12
151		(3α,4α,7α,7α)-Octahydro-1,3-dioxo-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenyl ester	3.397 LC	9
152		(3α,4α,7α,7α)-4-(Octahydro-1,3-dioxo-4,7-ethano-2H-pyrrolo[3,4-c]pyridin-2-yl)-1-naphthalenecarbonitrile	1.74 LC	11
153		(3α,4α,7α,7α)-4-(Octahydro-5-methyl-1,3-dioxo-4,7-ethano-2H-pyrrolo[3,4-c]pyridin-2-yl)-1-naphthalenecarbonitrile	1.71 LC	14

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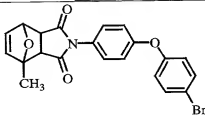
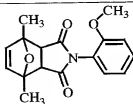
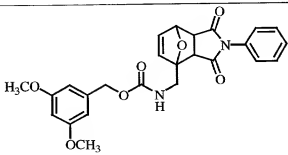
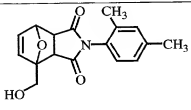
Ex. No.	Compound Structure	Compound Name	Retention Time Min./Molecular Mass	Pro. of Ex.
154		(3α,4α,7α,7α)-2-(4-cyano-1-naphthalenyl)octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenylmethyl ester	3.40 LC	10
155		(3α,4α,7α,7α)-4-(Octahydro-1,3-dioxo-4,7-ethano-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(trifluoromethyl)benzonitrile	1.74 LC	11
156		(3α,4α,7α,7α)-4-(Octahydro-5-methyl-1,3-dioxo-4,7-ethano-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(trifluoromethyl)benzonitrile	1.65 LC	14
157		(3α,4α,7α,7α)-2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenylmethyl ester	3.53 LC	10
158		(3α,4α,7α,7α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]tetrahydro-5-methyl-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione	2.95 LCMS	34

Ex. No.	Compound Structure	Compound Name	Retention Time Min/ Molecular Mass	Pro. of Ex.
159		(3α,4α,7α,7α)-Tetrahydro-5-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione	2.53 LCMS	34
160		(3α,4α,7α,7α)-Tetrahydro-5-methyl-2-(2-naphthalenyl)-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione	2.58 LCMS	34
161		(1α,2β,2α,5α,6β,6α)-Hexahydro-4-[3-(trifluoromethyl)phenyl]-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione	1.80 LCMS	28
162		(1α,2β,2α,5α,6β,6α)-4-(3,5-Dichlorophenyl)-hexahydro-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione	1.45 LCMS	28
163		(1α,2β,2α,5α,6β,6α)-Hexahydro-4-(4-nitro-1-naphthalenyl)-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione	1.52 LCMS	28
164		(1α,2β,2α,5α,6β,6α)-4-(3,4-Dichlorophenyl)-hexahydro-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione	3.21 LCMS	28

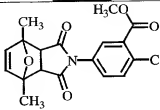
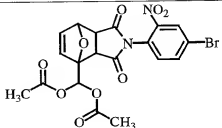
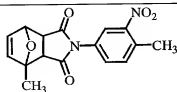
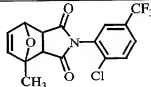
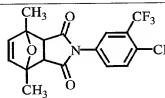
Examples 165 to 203

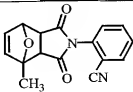
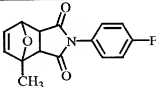
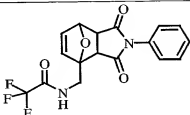
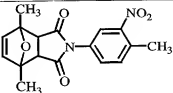
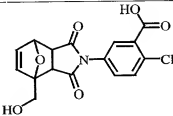
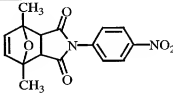
- Additional compounds of the present invention were prepared and are described further below in **Table 4**. **Table 4** sets forth the compound name and structure, as well as the Example number of the procedure on which the preparation of **Table 4** was based, for the compounds of Examples 165 to 203.

**Table 4**

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
165		2-[4-(4-Bromophenoxy)phenyl]-3a,4,7,7a-tetrahydro-4-methyl-4,7-epoxy-1H-isindole-1,3(2H)-dione	32
166		3a,4,7,7a-Tetrahydro-2-(2-methoxyphenyl)-4,7-dimethyl-4,7-epoxy-1H-isindole-1,3(2H)-dione	32
167		[(1,2,3,3a,7,7a-Hexahydro-2-phenyl-4,7-epoxy-4H-isindol-4-yl)methyl]carbamic acid (3,5-dimethoxyphenyl)methyl ester	21-26
168		2-(2,4-Dimethylphenyl)-3a,4,7,7a-tetrahydro-4-(hydroxymethyl)-4,7-epoxy-1H-	21-26

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
		isoindole-1,3(2H)-dione	
169		2-(1,3-Benzodioxol-5-yl)-3a,4,7,7a-tetrahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
170		4-[Bis(acetyloxy)methyl]-2-(3-bromophenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	21-26
171		N-[[1,2,3,3a,7,7a-Hexahydro-2-(2,4,6-trimethylphenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]-2,2-dimethylpropanamide	21-26
172		3a,4,7,7a-Tetrahydro-4-(hydroxymethyl)-2-[2-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	21-26
173		3a,4,7,7a-Tetrahydro-4-(hydroxymethyl)-2-(1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	21-26

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
174		2-Chloro-5-(1,3,3a,4,7,7a-hexahydro-4,7-dimethyl-4,7-epoxy-2H-isoindol-2-yl)benzoic acid methyl ester	32
175		4-[Bis(acetyloxy)methyl]-2-(4-bromo-2-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	21-26
176		3a,4,7,7a-Tetrahydro-4-methyl-2-(4-methyl-3-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
177		2-[2-Chloro-5-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
178		2-[4-Chloro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
179		2-(1,3,3a,4,7,7a-Hexahydro-4-methyl-4,7-epoxy-2H-isoindol-2-yl)benzonitrile	32
180		2-(4-Fluorophenyl)-3a,4,7,7a-tetrahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
181		2,2,2-Trifluoro-N-[(1,2,3,3a,7,7a-hexahydro-2-phenyl-4,7-epoxy-4H-isoindol-4-yl)methyl]acetamide	21-26
182		3a,4,7,7a-Tetrahydro-4,7-dimethyl-2-(4-methyl-3-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
183		2-Chloro-5-[1,3,3a,4,7,7a-hexahydro-4-(hydroxymethyl)-4,7-epoxy-2H-isoindol-2-yl]benzoic acid	21-26
184		3a,4,7,7a-Tetrahydro-4,7-dimethyl-2-(4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
185		3a,4,7,7a-Tetrahydro-2-(2-mercaptophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
186		3a,4,7,7a-Tetrahydro-2-[(phenylmethyl)thio]phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
187		[[2-(4-Chlorophenyl)-1,2,3,3a,7,7a-hexahydro-4,7-epoxy-4H-isoindol-4-yl]methyl]carbamic acid 2-methylpropyl ester	21-26
188		4-(1,1-Dimethylethyl)-N-[[1,2,3,3a,7,7a-hexahydro-2-(4-methylphenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]benzamide	21-26
189		2,4-Dichloro-N-[[1,2,3,3a,7,7a-hexahydro-2-(4-nitrophenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]benzamide	21-26



Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
190		<i>N</i> -[(2-(4-Chlorophenyl)-1,2,3,3a,7,7a-hexahydro-4,7-epoxy-4H-isoindol-4-yl)methyl]-2,4,6-trimethylbenzenesulfonamide	21-26
191		<i>N</i> -[(1,2,3,3a,7,7a-Hexahydro-2-(4-nitrophenyl)-4,7-epoxy-4H-isoindol-4-yl)methyl]-2,2-dimethylpropanamide	21-26
192		<i>N</i> -[(1,2,3,3a,7,7a-Hexahydro-2-phenyl-4,7-epoxy-4H-isoindol-4-yl)methyl]-2-phenoxyacetamide	21-26
193		[(1,2,3,3a,7,7a-Hexahydro-2-phenyl-4,7-epoxy-4H-isoindol-4-yl)methyl]carbamic acid 1,1-dimethylethyl ester	21-26
194		2-(2,4-Dichlorophenyl)- <i>N</i> -[(1,2,3,3a,7,7a-hexahydro-2-(4-nitrophenyl)-4,7-epoxy-4H-isoindol-4-yl)methyl]acetamide	21-26

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
195		<i>N</i> -[[1,2,3,3a,7,7a-hexahydro-2-(4-methylphenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]-3,5-dimethoxybenzamide	21-26
196		<i>N</i> -[[2-(4-chlorophenyl)-1,2,3,3a,7,7a-hexahydro-4,7-epoxy-4H-isoindol-4-yl]methyl]-2-nitrobenzenesulfonamide	21-26
197		(3α,4β,7β,7α)-Hexahydro-2-[(1 <i>S</i> )-1-phenylethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8
198		(3α,4β,7β,7α)-Hexahydro-2-[(1 <i>S</i> )-2-hydroxy-1-phenylethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8
199		(3α,4β,7β,7α)-2-[(1 <i>S</i> )-2-(Acetoxy)-1-phenylethyl]-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8

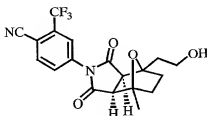
10024678.121901

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
200		(3α,4α,7α,7α)-3a,4,7,7a-Tetrahydro-2-[(1S)-1-phenylethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8
201		(3α,4β,7β,7α)-Hexahydro-2-[(1R)-1-phenylethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8
202		(3α,4β,7β,7α)-4-[[[(Octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)methyl]amino]benzoic acid.	8
203		(3α,4β,7β,7α)-Hexahydro-2-(4-morpholinylmethyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8

1061217-8/292001

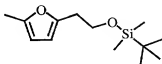
**Example 204**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[(Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (204D/25B)**



5

**A. 2-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-5-methylfuran (204A)**

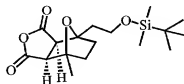


10

To a solution of compound **21A** (2.00 g, 15.9 mmol) in DMF (50 mL) was added imidazole (1.62 g, 23.9 mmol), followed by *tert*-butyldimethylsilyl chloride (2.63 g, 17.5 mmol). After 2 h at 25°C, the reaction was poured into diethyl ether (300 mL) and washed with water (1 x 100 mL), 1 N HCl (1 x 100 mL), water (1 x 100 mL), brine (1 x 50 mL) and dried over anhydrous MgSO<sub>4</sub>. Crude compound **204A** was analyzed by LCMS and NMR and determined to be pure enough to be carried on directly to the next step. HPLC: 100% at 4.347 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm).

20

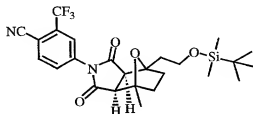
**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-7-methyl-4,7-epoxy-1H-isobenzofuran-1,3(2H)-dione (204B)**



25

- Compound **204A** (4.0 g, 18.9 mmol) and maleic anhydride (1.42 g, 14.5 mmol) were dissolved in dichloroethane (10 mL) and stirred at 25°C for 60 hours. The volatiles were then removed *in vacuo* and the resulting orange oil was dissolved in absolute ethanol (50 mL) and 10% Pd/C (1.00 g, cat.) was added. Hydrogen was then introduced via a balloon. After 3 h, the reaction was filtered through Celite rinsing with EtOAc and concentrated *in vacuo*. The crude anhydride was purified by rapid flash chromatography on SiO<sub>2</sub> eluting with acetone/chloroform (0 – 2 – 4% acetone) to give 1.30 g (3.82 mmol, 20%) of compound **204B** as a clear oil, in addition to 3.00 g (12.5 mmol, 66%) of the starting compound **204A**.
- 10 Characterization by proton NMR spectroscopy showed only the *exo* isomer. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 3.83 (2 H, t, *J* = 6.0 Hz), 3.22 (1 H, d, *J* = 8.2 Hz), 3.06 (1 H, d, *J* = 8.2 Hz), 1.70 – 2.25 (6 H, m), 1.55 (3 H, s), 0.82 (9 H, s), 0.00 (6 H, s).

- C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (**204C**)
- 15



- 20 Compound **204B** (0.250 g, 0.734 mmol) and 4-amino-2-trifluoromethylbenzonitrile (0.124 g, 0.668 mmol) were suspended in dry toluene (2.0 mL) in a sealed tube. MgSO<sub>4</sub> (0.200 g) and triethylamine (0.5 mL) were then added and the tube was sealed and placed in an oil bath at 125°C. After 40 h, the reaction was cooled to 25°C, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on SiO<sub>2</sub> eluting with CH<sub>2</sub>Cl<sub>2</sub> to give 0.111 g (0.281 mmol, 30%) of compound **204C** as a yellow solid. HPLC: 92% at 4.203 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes
- 25

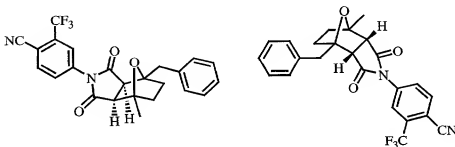
containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ESI):  $m/z$  531.1  $[M+Na]^+$ .

**D. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (**204D**)**

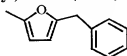
Compound **204C** (0.031 g, 0.061 mmol) was dissolved in THF (0.5 mL) and transferred to a polypropylene container followed by cooling to 0°C. HF·pyridine (~47% HF, 0.1 mL) was then added. After 15 min, the reaction was complete as determined by LC and was poured into cold sat. aqueous NaHCO<sub>3</sub>. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were washed with 1 N HCl (1 x 20 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Compound **204D** was isolated as a yellow oil and compared to the material prepared in Example 25. No purification was necessary.

**Example 205**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-4-[Octahydro-4-methyl-1,3-dioxo-7-(phenylmethyl)-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (**205Ci** and **205Cii**, respectively)**



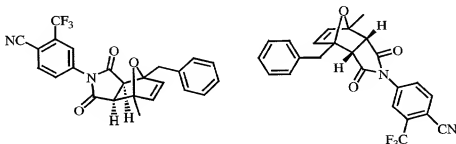
**A. 2-Methyl-5-(phenylmethyl)-furan (**205A**)**



*n*-BuLi (1.8 mL, 4.51 mmol, 2.5 M in hexane) was added to a solution of 2-methylfuran (0.37 mL, 4.10 mmol) in anhydrous THF (3 mL) at -25 °C. The resulting solution was stirred at room temperature for 3 h and then cooled to

–15°C. Benzyl bromide (0.59 mL, 4.92 mmol), which was passed through a plug of aluminum oxide, was added and the solution was warmed to rt and stirred overnight. Saturated NH<sub>4</sub>Cl solution (5 mL) was added and the mixture was stirred for 1 h. The reaction mixture was then extracted with ether (2 x 5 mL) and the combined organic extracts were dried and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexanes gave 323 mg (1.88 mmol, 46%) of compound **205A** as colorless oil. HPLC: 95% at 3.72 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm) and about 400 mg mixture of product and benzyl bromide (~2:1 by HPLC).

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-4-[Octahydro-4-methyl-1,3-dioxo-7-(phenylmethyl)-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (**205Bi** and **205Bii**, respectively)**



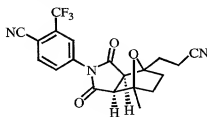
A solution of compound **205A** (124 mg, 0.72 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (290 mg, 1.09 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred at room temperature. After 4 days, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub> gave 62 mg (0.14 mmol, 20%) of a mixture of compounds **205Bi** and **205Bii** as a white solid, which was used directly in the next step. HPLC: 93% at 3.69 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

- C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- and (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-4-[Octahydro-4-methyl-1,3-dioxo-7-(phenylmethyl)-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)-benzonitrile (**205Ci** and **205Cii**, respectively)

- 5 A solution of a mixture of compounds **205Bi** and **205Bii** (62 mg, 0.14 mmol) and 10% Pd/C (12 mg, cat.) in EtOH (3.5 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 35% EtOAc/hexanes gave 22 mg (0.05 mmol, 35%) of
- 10 compound **205Ci** and 12 mg (0.027 mmols, 19%) of compound **205Cii**. Compound **205Ci**: HPLC: 98% at 3.75 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 458.2 [M+NH<sub>4</sub>]<sup>+</sup>. Compound **205Cii**: HPLC: 97% at 3.78 min (retention time) (YMC S5 ODS column 4.6 x 50
- 15 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 473.45 [M+CH<sub>3</sub>OH]<sup>+</sup>.

#### Example 206

- 20 (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-propanenitrile (**206**)



- A solution of compound **36** (34 mg, 0.074 mmol) and NaCN (24 mg, 0.49 mmol) in DMSO (1 mL) was heated at 100°C for 0.5 h. After cooling,
- 25 the reaction mixture was poured into H<sub>2</sub>O (5 mL) and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with H<sub>2</sub>O (2 x 5 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under

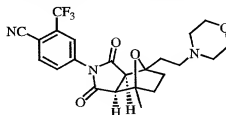


reduced pressure. Purification by flash chromatography on SiO<sub>2</sub> eluting with 50% EtOAc/hexanes followed by reverse phase preparative HPLC [30.41 min (retention time) (YMC S5 ODS 30 X 250 mm, 10-90% aqueous methanol over 30 minutes containing 0.1% TFA, 25 mL/min, monitoring at 220 nm)] gave 6.6 mg (0.016 mmol, 22%) of compound **206** as a white solid. HPLC: 99% at 2.89 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 402.1 [M-H]<sup>+</sup>.

10

### Example 207

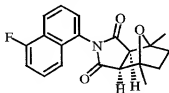
(3a*c*,4*b*,7*b*,7a*o*)-4-[Octahydro-4-methyl-7-[2-(4-morpholinyl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, trifluoroacetate (1:1) (207)



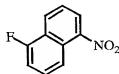
15

A solution of compound **36** (15.6 mg, 0.0341 mmol) and morpholine (6.0  $\mu$ L, 0.068 mmol) in toluene (1 mL) was heated at 100°C overnight. After cooling, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on SiO<sub>2</sub> eluting with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> followed by reverse phase preparative HPLC [23.96 min (retention time) (YMC S5 ODS 30 x 250 mm, 10-90% aqueous methanol over 30 minutes containing 0.1% TFA, 25 mL/min, monitoring at 220 nm)] gave 8.7 mg (0.015 mmol, 44%) of compound **207** (TFA salt) as a white solid. HPLC: 99% at 2.02 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 464.3 [M+H]<sup>+</sup>.

25

Example 208(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(5-Fluoro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (208C)

## 5    A.    1-Fluoro-5-nitronaphthalene (208A)

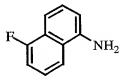


To a solution of 6 N HCl (12 mL) was added 1.47 g (7.83 mmol) of finely powdered 5-nitro-1-naphthylamine, as described in *J. Chem. Soc.* 1187 (1949). The mixture was cooled to 0°C and a cold solution of NaNO<sub>2</sub> (547 mg, 7.93 mmol) in 2 mL H<sub>2</sub>O was added slowly so that the temperature was kept near 0°C. After the addition was complete, the reaction mixture was stirred for 30 min and filtered. The filtrate was cooled to 0°C and treated with cold 4.5 M NaBF<sub>4</sub> solution (5 mL) to give complete precipitation of the diazonium borofluoride. The mixture was kept at 0°C for 30 min before it was filtered and the precipitates were washed with cold 4.5 M NaBF<sub>4</sub> solution (5 mL), ice-cold ethanol (10 mL) and Et<sub>2</sub>O (20 mL). The obtained solids were air dried to yield 1.74 g (77%) of the corresponding diazonium salt.

To 1.70 g (5.92 mmol) of the above diazonium borofluoride was added 5 g of sand and the components were thoroughly mixed. The reaction mixture was heated cautiously under reduced pressure until decomposition set in. Toward the end of the reaction the flask was further heated for 30 min to 130°C to assure complete conversion. After cooling the reaction mixture was dissolved in acetone and the contents were preabsorbed on silica gel. Purification was achieved by flash

chromatography on silica gel, eluting with 0 to 10% EtOAc in hexanes to give 449 mg (2.35 mmol, 40%) of compound **208A** as a white solid.

**B. 1-Amino-5-fluoronaphthalene (208B)**



5

A solution of compound **208A** (62 mg, 0.32 mmol) in 1 mL EtOH containing 0.1 mL 12 N HCl was heated to reflux. Iron powder (62 mg, 1.11 mmol) was added in small portions and heating was continued for 2 h. The mixture was cooled, neutralized with 1 N NaOH solution and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to leave a residue which was purified by flash chromatography on silica gel eluting with 40 to 80% EtOAc in hexanes to give 42 mg (0.26 mmol, 80%) of compound **208B** as a yellow solid.

10

15

**C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(5-Fluoro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (208C)**

Compound **208B** (42 mg, 0.26 mmol), compound **20A** (54 mg, 0.27 mmol),  $\text{MgSO}_4$  (69 mg, 0.58 mmol) and triethylamine (191  $\mu\text{L}$ , 1.37 mmol) were taken up in 2 mL of toluene and placed in a sealed tube. The sealed tube was heated at 135°C for 14 h. The cooled reaction mixture was filtered through a short pad of Celite eluting with  $\text{CH}_2\text{Cl}_2$  and the solvent was removed under reduced pressure. The residue was purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min) to give 15 mg (0.044 mmol, 17%) of compound **208C** as a light yellow solid. HPLC: 16% at 2.96 min & 77% at 3.06 min (atropisomers, retention time)

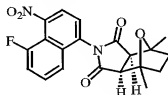
25

(YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  340.2  $[M+H]^+$ .

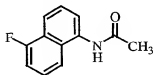
5

**Example 209**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(5-Fluoro-4-nitro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (209C)**



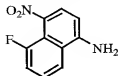
**A. N-(5-Fluoro-1-naphthalenyl)acetamide (209A)**



10

A solution of 141 mg (0.74 mmol) of compound **208A** in 2 mL of AcOH was heated to reflux and treated with small portions of iron powder (118 mg, 2.11 mmol). The mixture was kept at reflux for 15 min before 73  $\mu$ L (0.78 mmol) of  $Ac_2O$  was added. After an additional 15 min at reflux, the mixture was cooled and filtered eluting with  $CH_2Cl_2$ . The filtrate was then concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with 20 to 50% EtOAc in to give 145 mg (0.71 mmol, 97%) of compound **209A** as a white solid.

**20 B. 1-Amino-5-fluoro-4-nitronaphthalene (209B)**



Compound **209A** (133 mg, 0.645 mmol) was dissolved in 1 mL AcOH and the resulting solution was cooled to 10°C. At this temperature, 80.0  $\mu$ L (2.00 mmol) of red fuming  $HNO_3$  was added and stirring was continued

for 15 min before the reaction was quenched by the addition of crushed ice. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic phases were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The resulting residue was dissolved in 3 mL EtOH, heated to reflux and  
 5 treated with 0.5 mL of 40% aqueous NaOH solution. Stirring was continued for 15 min before the reaction was cooled and diluted with  $\text{H}_2\text{O}$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic phases were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel, eluting with  
 10 40 to 70% EtOAc in hexane to afford 36 mg (0.17 mmol, 27%) of compound **209B** as a yellow solid.

**C.  $3\alpha,4\beta,7\beta,7\alpha$ -2-(5-Fluoro-4-nitro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (209C)**

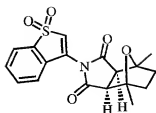
15

Compound **209B** (36 mg, 0.18 mmol) was reacted in a sealed tube with compound **20A** (38 mg, 0.19 mmol),  $\text{MgSO}_4$  (46 mg, 0.39 mmol) and  $\text{Et}_3\text{N}$  (128  $\mu\text{L}$ , 0.920 mmol) in 250  $\mu\text{L}$  toluene according to the above procedure described in example **208C** to give, after purification by reverse  
 20 phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min), 27 mg (0.070 mmol, 39%) of compound **209C** as a yellow solid. HPLC: 8% at 2.88 min & 84% at 3.06 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4  
 25 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  402.0  $[\text{M}+\text{H}]^+$ .

**Example 210**

30

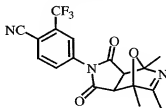
**$3\alpha,4\beta,7\beta,7\alpha$ -2-(1,1-Dioxidobenzo[b]thiophen-3-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (210)**



mCPBA (160 mg, 0.641 mmol, 70% pure) was added to a solution of  
 compound **134** (70.0 mg, 0.214 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at rt. After the  
 starting material was consumed, the reaction was quenched with sat.  
 5  $\text{NaHCO}_3$ , and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with  
 1 N NaOH, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to  
 give 63.9 mg (0.178 mmol, 83%) of compound **210** as a white solid. HPLC:  
 99% at 3.81 min (retention time) (YMC S5 ODS column 4.6 x 50 mm  
 eluting with 10-90% aqueous methanol over 4 minutes containing 0.2%  
 10 phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  360.0  
 $[\text{M}+\text{H}]^+$ .

#### Example 211

15 **4-(1,3,3a,4,7,7a-Hexahydro-4,6,7-trimethyl-1,3-dioxo-4,7-epoxy-2H-**  
**pyrrolo[3,4-c]pyridin-2-yl)-2-(trifluoromethyl)benzonitrile (211)**



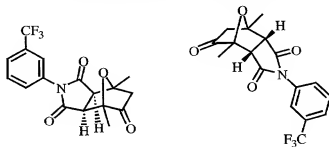
2,4,5-Trimethyl oxazole (0.48 mL, 4.14 mmol) was dissolved in  
 toluene (2.0 mL) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-  
 20 trifluoromethylbenzonitrile (1.00 g, 3.76 mmol) was added. The reaction  
 mixture was stirred at 75°C under nitrogen for 2.5 hrs. The solution was  
 cooled to room temperature and the resulting precipitate was filtered and  
 rinsed with toluene to give 0.51 g (35%) of compound **211** as a light grey  
 solid. NMR analysis revealed that compound **211** was one isomer  
 25 (exo/endo) however the identity of the isomer could not be determined by

NMR analysis. HPLC: 100% at 2.85 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  378.42  $[M+H]^+$ .

5

### Example 212

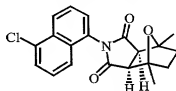
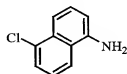
**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Tetrahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3,5(2H,4H)-trione & (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-Tetrahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3,5(2H,4H)-trione (212i & 212ii, respectively)**



2,2-Dimethyl-3(H)-furanone (0.500 g, 4.46 mmol) and 1-[3-(trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (1.07 g, 4.46 mmol, prepared as described in Example 1B) were suspended in toluene (20 mL) in a sealed tube. The mixture was heated at 110°C for 4 h and then cooled to 25°C followed by concentration *in vacuo*. The resulting residue was purified by flash chromatography on SiO<sub>2</sub> eluting with methylene chloride to yield 0.411 g (26%) of compound **212i** as a white solid and 0.193 g (12%) of compound **212ii** as a white solid. The structural assignments were confirmed by 1-D NOE proton NMR experiments. Compound **212i**: HPLC: 100% at 2.817 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  376.0  $[M + Na]^+$ . Compound **212ii**: HPLC: 100% at 3.013 min (retention time) (YMC S5

ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  354.02  $[M+H]^+$ .

5

Example 213(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(5-Chloro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (213B)10    **A.    1-Amino-5-chloronaphthalene (213A)**

To a solution of 1.74 g (6.06 mmol) of the diazonium borofluoride (described in Example **208A**) in acetone (7 mL) was added 693 mg (7.00 mmol) of CuCl in small portions. After the evolution of nitrogen had ceased the acetone was removed under reduced pressure and the residue was taken up in  $CH_2Cl_2$  (30 mL). The organic phase was washed with  $H_2O$  (30 mL), dried over  $MgSO_4$ , concentrated *in vacuo* and finally purified by flash chromatography (silica gel, EtOAc in hexane 0 to 15% ) to give 754 mg (70%) of 1-chloro-5-nitronaphthalene.

20    The above synthesized 1-chloro-5-nitronaphthalene (540 mg, 2.6 mmol) was dissolved in 10 mL AcOH, followed by treatment with 415 mg (7.43 mmol) iron powder and subsequently acylated with  $Ac_2O$  (0.26 mL, 2.73 mmol) according to the procedure described in Example **209A** to give 543 mg (95%) of 1-acetamino-5-chloronaphthalene.

25    A solution of the above synthesized 1-acetamino-5-chloronaphthalene (52 mg, 0.24 mmol) in 3 mL EtOH was heated to reflux



and treated with 0.5 mL 40% aqueous NaOH solution. The mixture was refluxed until no more starting material could be detected, cooled and concentrated under reduced pressure. The residue was taken up in  $\text{CH}_2\text{Cl}_2$  (50 mL) and was washed with  $\text{H}_2\text{O}$  (25 mL). The organic layer was dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to leave 41 mg (98%) of compound **213A** as a white solid.

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(5-Chloro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (213B)**

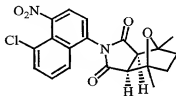
10

Compound **213A** (24 mg, 0.14 mmol) was reacted in a sealed tube with compound **20A** (29 mg, 0.15 mmol),  $\text{MgSO}_4$  (36 mg, 0.30 mmol) and  $\text{Et}_3\text{N}$  (100  $\mu\text{L}$ , 0.710 mmol) in 250  $\mu\text{L}$  toluene according to the procedure described in Example **208C** to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min), 27 mg (40%) of compound **213B** as a white solid. HPLC: 98% at 1.82 min (retention time) (YMC S5 TurboPack Pro column 4.6 x 33 mm eluting with 10-90% aqueous methanol over 2 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  356.4  $[\text{M}+\text{H}]^+$ .

20

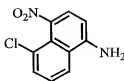
**Example 214**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(5-Chloro-4-nitro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (214B)**



25

**A. 1-Amino-5-chloro-4-nitronaphthalene (214A)**



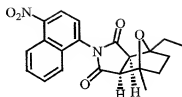
1-Acetamino-5-chloronaphthalene (150 mg, 0.68 mmol, prepared as described in Example 213A) was dissolved in 1 mL AcOH and treated with 82  $\mu$ L of red fuming  $\text{HNO}_3$  and subsequently deacylated with 1 mL 40% aqueous NaOH solution in 3 mL EtOH according to the procedure described in Example 209A to yield 49 mg (32%) of compound 214A as a yellow solid.

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(5-Chloro-4-nitro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (214B)**

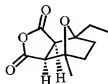
Compound 214A (27 mg, 0.12 mmol) was reacted in a sealed tube with compound 20A (26 mg, 0.13 mmol),  $\text{MgSO}_4$  (32 mg, 0.27 mmol) and  $\text{Et}_3\text{N}$  (88  $\mu$ L, 0.63 mmol) in 250  $\mu$ L toluene according to the procedure described in Example 208C to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min) 22 mg (45%) of compound 214B as a yellow solid. HPLC: 24% at 3.06 min & 76% (45%) of compound 214B as a yellow solid. HPLC: 24% at 3.06 min & 76% (45%) of compound 214B as a yellow solid. HPLC: 24% at 3.06 min & 76% (45%) of compound 214B as a yellow solid. HPLC: 24% at 3.06 min & 76% (45%) of compound 214B as a yellow solid. HPLC: 24% at 3.06 min & 76% (45%) of compound 214B as a yellow solid. MS (ES):  $m/z$  418.0  $[\text{M}+\text{NH}_4]^+$ .

**Example 215**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-Ethylhexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (215B)**



**A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-Ethylhexahydro-7-methyl-4,7-epoxyisobenzofuran-1,3-dione (215A)**



- 5 2-Ethyl-5-methylfuran (1.89 mL, 15.3 mmol) was dissolved in methylene chloride (10 mL) and maleic anhydride (1.00 g, 10.2 mmol) was added. The reaction was stirred at 25°C for 18 h and then concentrated *in vacuo*. The resulting crude bicycle was dissolved in EtOAc (50 mL) and 10% Pd/C (0.40 g) was added. Hydrogen was then introduced via a
- 10 balloon. After 4 h, the reaction was filtered through Celite, rinsing with EtOAc. Concentration *in vacuo* gave the crude compound **215A** (1.93 g) as a white solid. This material was taken on directly to the next reaction without purification.

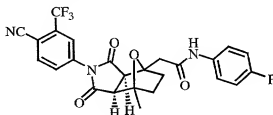
**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-Ethylhexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (215B)**

- Compound **215A** (0.168 g, 0.798 mmol) and 1-amino-4-nitronaphthalene (0.10 g, 0.53 mmol) were suspended in toluene (0.8 mL)
- 20 and TEA (0.2 mL) and magnesium sulfate (0.1 g) were added. The mixture was heated at 135°C in a sealed tube for 18 h. The reaction was then cooled to rt and filtered, rinsing with chloroform. Concentration gave the crude product which was purified by preparative TLC on SiO<sub>2</sub> eluting with methylene chloride. This gave 0.077 g (0.20 mmol, 38%) of compound
- 25 **215B** as a yellow solid. HPLC: 100% at 3.260 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over

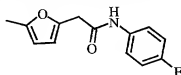
4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  381.05  $[M+H]^+$ .

### Example 216

- 5      (3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-2-(4-Cyano-1-naphthalenyl)-N-(4-fluorophenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetamide (216B)



- 10    A.    N-(4-Fluorophenyl)-5-methyl-2-furanacetamide (216A)



- 5-Methyl-2-furanacetic acid (1.00 g, 7.14 mmol, synthesized as described WO 9507893, Example 19) was dissolved in  $CH_3CN$ /DMF (4:1, 25 mL), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.37 g, 7.14 mmol) and 1-hydroxy-7-azabenzotriazole (0.972 g, 7.14 mmol) were then added followed by 4-fluoroaniline (0.676 mL, 7.14 mmol). After 3 h, the reaction was diluted with EtOAc (150 mL) and washed with 1 N HCl (1 x 30 mL), sat. aq.  $NaHCO_3$  (1 x 30 mL), brine (1 x 40 mL) and dried over sodium sulfate. Compound **216A** (1.58 g, 95%) was isolated as a yellow foam after concentration *in vacuo*. No further purification was necessary. HPLC: 78% at 2.647 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

25

**B. 3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)-N-(4-fluorophenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetamide (216B)**

5 Compound **216A** (0.200 g, 0.858 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (0.164 g, 0.616 mmol) were dissolved in benzene and heated at 60°C for 14 h. The reaction was then cooled and concentrated *in vacuo*. The resulting orange oil was dissolved in EtOAc (15 mL) and 10% Pd/C (0.050 g) was added. Hydrogen  
10 was then introduced via a balloon. After 3 h, the reaction was filtered through Celite rinsing with EtOAc and concentrated *in vacuo*. The resulting crude material was purified by preparative TLC on silica eluting with 5% acetone in methylene chloride to give 0.166 g (54%) of compound **216B** as a white solid. NMR spectroscopy showed only a single isomer  
15 which was determined to be *exo* by NOE experiments. HPLC: 95% at 3.200 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 484.0 [M+ H]<sup>+</sup>.

20

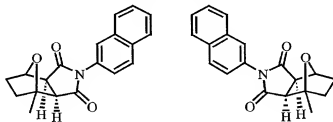
**Example 217**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4-methyl-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione, faster eluting enantiomer &**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4-methyl-2-(2-naphthalenyl)-4,7-epoxy-**

25 **1H-isoindole-1,3(2H)-dione, slower eluting enantiomer (217i &**

**217ii, respectively)**

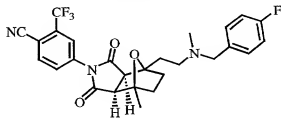


Racemic compound **137** was separated into the individual antipodes by chiral reverse phase liquid chromatography. A Chiralpak AD-R column (4.6 x 250 mm) was used eluting with 70% acetonitrile/30% water at 1 mL/min. UV detection at 220 nm was used. The faster eluting isomer, compound **217i** (retention time = 15.66 min), was found to be 99.9% ee and the slower eluting isomer, compound **217ii** (retention time = 15.66 min) was 99.6% ee by analytical chiral reverse phase chromatography.

10

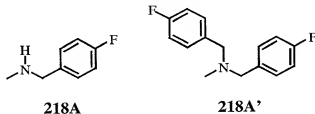
**Example 218**

**(3aα,4β,7β,7aα)-4-[4-[2-[(4-Fluorophenyl)methyl]methylamino]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile**

**(218B)**

15

**A. (4-Fluorobenzyl)methylamine & Bis(4-fluorobenzyl)methylamine (218A & 218A')**



Compounds **218A** & **218A'** were made in accordance with the procedure described by Singer et al. *J. Med. Chem.* **29**, 40-44 (1986). 4-Fluorobenzyl bromide (189 mg, 1.00 mmol) was refluxed in a solution of ethanol (1.5 mL) and methylamine (5 mL, 2 M solution in MeOH) for 3 h. An additional portion of methylamine (2 mL) was added and the mixture was refluxed for an additional hour. The solution was cooled and

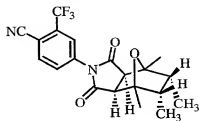
concentrated *in vacuo*, and the residue was dissolved in a mixture of 2 N HCl (3 mL) and ether (1.5 mL). The layers were separated and the aqueous layer was extracted with an additional portion of ether. The aqueous solution was chilled to 0°C, titrated to pH 11 with NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give 120 mg of a 2.5:1 mixture of compounds **218A** and compound **218A'** respectively. The crude mixture was taken on without further purification.

**10 B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[[ (4-Fluorophenyl)methyl]-methylamino]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (**218B**)**

A solution of compound **36** (34.3 mg, 0.075 mmol) and compounds **218A** & **218A'** (21 mg, ~0.088 mmol (of **218A**)) in toluene (0.4 mL) was heated at 100°C overnight. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 25% acetone/75% CH<sub>2</sub>Cl<sub>2</sub> gave 30 mg (0.058 mmol, 78%) of **218B** as a yellow solid. HPLC: 99% at 2.46 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm). MS (ES): m/z 516.26 [M+ H]<sup>+</sup>.

Example 219

**25 (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-4,5,6,7-tetramethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (**219D**)**



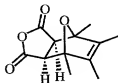
## A. 2,3,4,5-Tetramethylfuran (219A)



Compound **219A** was made in accordance with the procedures  
 5 described in Hancock et al. *J. Org. Chem.* **42**,1850-1856 (1977) &  
 Amarnath et al. *J. Org. Chem.*, **60**, 301-307 (1995). 2-Propanone (100 mL,  
 1.1 mol) was refluxed over  $\text{PbO}_2$  (26.7 g, 0.112 mol) for 28 h. After cooling  
 to rt, the reaction mixture was filtered and the residue was washed with  
 10 acetone. The filtrate was concentrated under reduced pressure to remove  
 the acetone and then distilled at 20 Torr. The fraction that came over  
 between 100-120°C was collected to give 6.75 g (42.5%) of 3,4-  
 dimethylhexane-2,5-dione as a light yellow oil.

A solution of 3,4-dimethylhexane-2,5-dione (3.00 g, 21.1 mmol) and  
 p-toluenesulfonic acid (401 mg, 2.11 mmol) in benzene (30 mL) was heated  
 15 to reflux in a Dean-Stark trap overnight. The reaction mixture was  
 distilled at atmospheric pressure to remove the excess benzene. The  
 remaining mixture was transferred to a smaller flask and distilled at  
 atmospheric pressure. The fraction that came over between 80-100°C was  
 collected to give 509 mg (19%) of compound **219A** as a light yellow oil.

20

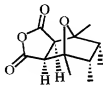
B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-Ethyl-3a,4,7,7a-tetrahydro-4,5,6,7-tetramethyl-4,7-epoxyisobenzofuran-1,3-dione (219B)

A solution of compound **219A** (400 mg, 3.22 mmol) and maleic  
 25 anhydride (442 mg, 4.51 mmol) in  $\text{Et}_2\text{O}$  (1.5 mL) was stirred at rt  
 overnight. The reaction mixture was then placed in freezer for 5 days,  
 after which time the resulting crystals were collected and dried to give



0.26 g (37%) of compound **219B** as tan crystals. The crude compound **219B** was taken on to the next step without further purification.

- 5 C. (3 $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,6 $\alpha$ ,7 $\beta$ ,7 $\alpha$ )-4-Ethylhexahydro-4,5,6,7-tetramethyl-4,7-epoxyisobenzofuran-1,3-dione (**219C**)



10 A solution of compound **219B** (120 mg, 0.545 mmol) and 10% Pd/C (24 mg, cat.) in EtOAc (2 mL) was stirred under a balloon of hydrogen at room temperature overnight. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 100 mg (0.446 mmol, 82%) of compound **219C** as a white solid, which was carried on with no further purification.

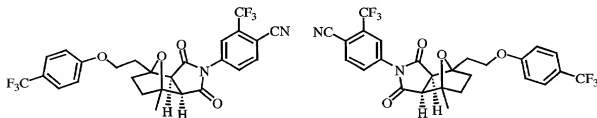
- 15 D. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-4,5,6,7-tetramethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (**219D**)

20 A solution of compound **219C** (44.4 mg, 0.2 mmol), 5-amino-2-cyanobenzotrifluoride (45 mg, 0.24 mmol), TEA (0.04 mL) and MgSO<sub>4</sub> (20 mg) in toluene (0.2 mL) was heated at 135°C overnight. The reaction mixture was cooled to room temperature, filtered and then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/hexanes followed by washing the resulting  
25 solid with MeOH gave 17 mg (0.043 mmol, 22%) of compound **219D** as a white solid. HPLC: 90% at 3.11 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm). MS (ES): m/z 391.2 [M-H].

Example 220

(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, faster eluting antipode &

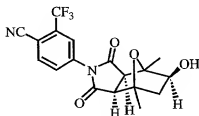
(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, slower eluting enantiomer (220i & 220ii, respectively)



Racemic compound **35** was separated into the individual antipodes by chiral normal phase liquid chromatography. A Chiralpak AD column (50 x 500 mm) was used eluting with 85% hexanes/7.5% methanol/7.5% ethanol, at 50mL/min. UV detection at 220 nm was used. The faster eluting isomer compound **220i** (retention time = 55.86 min) was found to have 95.8% ee ( $[\alpha]_D^{25} = -53.02^\circ$ , C = 3.134 mg/cc in  $\text{CH}_2\text{Cl}_2$ ) and the slower eluting isomer compound **220ii** (retention time = 62.86 min) was 86% ee ( $[\alpha]_D^{25} = +48.74^\circ$ , C = 2.242 mg/cc in  $\text{CH}_2\text{Cl}_2$ ) by analytical chiral normal phase chromatography.

Example 221

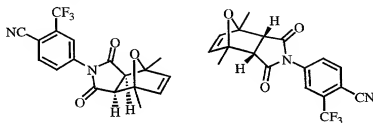
(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221B)



5

- A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221Ai) & (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-4-(hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221Aii)

10



- A solution of 2,5-dimethylfuran (0.800 mL, 7.51 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (synthesized as described in Example 1B, using 4-cyano-3-trifluoromethylaniline in place of 4-bromo-3-methylaniline) (1.00 g, 3.75 mmol) in benzene (4 mL) was heated at 60°C overnight. The reaction mixture was concentrated under reduced pressure and placed on a high vacuum pump until the oil solidified to give a 3:1 mixture (determined by LC and NMR) of compounds 221Ai & 221Aii, respectively, as a brown solid, which was used directly in the next step without further purification.

20

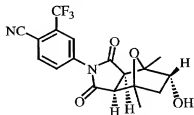
**B. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221B)**

- 5  $\text{BH}_3 \cdot \text{THF}$  (3.75 mL, 3.75 mmol, 1M in THF) was added to a solution of crude compounds **221Ai** & **221Aii** (3.75 mmol) in THF (12.5 mL) at 0°C. After the starting material was consumed the reaction mixture was concentrated under reduced pressure. The resulting residue was then dissolved in toluene (12.5 mL),  $\text{Me}_3\text{NO}$  (845 mg, 11.2 mmol) was added and the mixture was heated to reflux overnight. The reaction mixture was then cooled to rt, added to  $\text{H}_2\text{O}$  and extracted with EtOAc (3X). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash chromatography on  $\text{SiO}_2$  eluting with 75% EtOAc/hexanes gave 0.354 g (25%) of compound **221B** as a tan powder. HPLC: 90% at 2.45 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  381.11  $[\text{M}+\text{H}]^+$ .

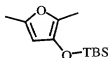
20

**Example 222**

**(3 $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (222D)**

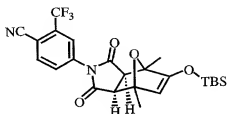


- A. 3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,5-dimethylfuran (222A)**



2,5-Dimethyl-3(3H)-furanone (2.00 g, 17.8 mmol) was dissolved in methylene chloride (180 mL). TEA (7.43 mL, 53.5 mmol) was added followed by TBSOTf (4.92 mL, 21.4 mmol) at 25°C. After 1 h, the reaction was concentrated *in vacuo* and the resulting slurry was run through a silica gel column conditioned with 3% TEA in hexanes. The product was eluted with 3% TEA/hexanes to give 3.6 g (89%) of compound **222A** as an orange oil which was used directly in subsequent reactions.

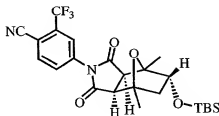
**B.** (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,3,3a,4,7,7a-hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-2-(trifluoromethyl)benzonitrile (**222B**)



4-(2,5-Dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (1.00 g, 3.85 mmol) was dissolved in benzene (5.0 mL) and the compound **222A** (1.30 g, 5.77 mmol) was added. The reaction mixture was warmed to 60°C for 2 h and then cooled to 25°C. The solution was then concentrated *in vacuo* to give compound **222B** as a yellow oil which was carried on to the next reaction without purification. HPLC: 60% at 4.013 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**C.** (3 $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,7 $\beta$ ,7 $\alpha$ )-4-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-4,7-dimethyl-1,3-

**dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-  
(trifluoromethyl)benzonitrile (222C)**



5

Crude compound **222B** (3.85 mmol) was dissolved in ethyl acetate (75 mL) and 10% Pd/C (1.20 g) was added. Hydrogen was then introduced via a balloon. After 24 h, the reaction was filtered through Celite rinsing with ethyl acetate and concentrated *in vacuo* to give a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with methylene chloride/acetone (0% - 1% - 2% acetone) to give 0.710 g (35%) compound **222C** as a yellow solid. HPLC: 100% at 4.160 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 517.6 [M+Na]<sup>+</sup>.

15

**D. (3 $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (222D)**

20

Compound **222C** (0.040 g, 0.081 mmol) was dissolved in THF (1.0 mL) and HF•Pyridine (0.5 mL) was added. After 2 h, the reaction was carefully poured into cold saturated aq. NaHCO<sub>3</sub>. The mixture was then extracted with methylene chloride (3 x 10 mL). The combined organics were washed with 1 N HCl (1 x 10 mL) and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.031 g (10%) compound **222D** as a yellow solid. NOE experiments confirmed the assigned isomer. HPLC:

25

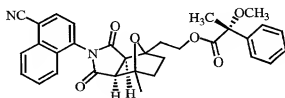
98% at 2.777 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  403.06  $[M+Na]^+$ .

5

**Example 223**

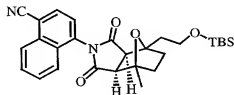
**( $\alpha R$ )- $\alpha$ -Methoxybenzeneacetic acid, 2-[ (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-ylethyl ester (223C)**

10



**A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[[ (1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (223A)**

15



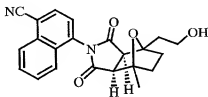
A solution of 4-amino-1-naphthalenecarbonitrile (19.2 g, 114 mmol) and maleic anhydride (14.0 g, 113 mmol) in AcOH (230 mL) was heated at 115°C for 12 h. After cooling to rt, the reaction mixture was concentrated under reduced pressure then diluted with  $CH_2Cl_2$  (2.5 L). The organic layer was washed 3X with  $H_2O$  (3 L), 1X with sat. aq.  $Na_2CO_3$  (1 L) and 1X with brine (1 L), dried over  $MgSO_4$  and concentrated to ~200 mL under reduced pressure. Purification by flash chromatography on cation exchange resin (60 g, CUBX13M6 from United Chemical Technologies)

25

eluting with  $\text{CH}_2\text{Cl}_2$  gave 25.0 g (88%) of 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile as a yellow solid. HPLC: 96% at 2.48 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  249.25  $[\text{M}+\text{H}]^+$ .

4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (1.00 g, 4.03 mmol) was suspended in benzene (6.0 mL) in a sealed tube and compound **204A** (1.11 g, 5.24 mmol) was added. The reaction was heated at 60°C for 16 h and then cooled to 25°C. The benzene was removed *in vacuo* to give a yellow solid. The solid was dissolved in ethyl acetate (40 mL) and Pd/C (10% Pd, 0.300 g) was added. Hydrogen was then introduced via a balloon. After 4 h, the reaction was filtered through Celite rinsing with ethyl acetate. Concentration *in vacuo* gave a pale yellow solid which was purified by flash chromatography on silica gel eluting with acetone/chloroform (0% - 1.5% - 3% acetone) to give 1.53 g (77%) compound **223A** as a yellow foam. HPLC: 86% at 4.173 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**B.** (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile (**223B**)



Compound **223A** (1.37 g, 2.97 mmol) was dissolved in THF (8.0 mL) and transferred to a polypropylene bottle and cooled to 0°C. HF•Pyridine



(2.0 mL) was then added. After 20 min, the reaction was carefully poured into cold sat. aq. sodium bicarbonate and extracted with methylene chloride (3 x 30 mL). The organics were then washed with 1 N HCl and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.99 g (89%) the compound **223B** as a yellow foam which was not purified further. HPLC: 96% at 2.443 and 2.597 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  399.02  $[M+Na]^+$ .

10

C. ( $\alpha R$ )- $\alpha$ -Methoxybenzeneacetic acid, 2-[(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl ester (**223C**)

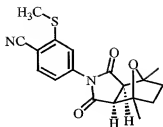
Compound **223B** (0.200 g, 0.575 mmol) was added to a solution of WSDCC (0.138 g, 0.719 mmol) and (*R*)-mandelic acid (0.096 g, 0.57 mmol) in dichloromethane (6.0 mL). 4-DMAP (0.005 g) was then added and the reaction was stirred at 25°C for 4 h. The mixture was then diluted with dichloromethane, washed with 1 N HCl (2 x 10 mL) followed by sodium bicarbonate (1 x 10 mL) and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.220 g (71%) compound **223C** as a yellow solid which was not purified further. HPLC: 100% at 3.283 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  547.26  $[M+Na]^+$ .

25

Example 224

(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(Methylthio)-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile (**224**)

30



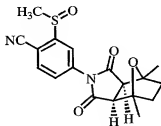
4-Amino-2-(methylthio)benzonitrile (100 mg, 0.609 mmol, synthesized as described in EP 40931 A1) was reacted in a sealed tube with compound **20A** (131 mg, 0.668 mmol),  $\text{MgSO}_4$  (161 mg, 1.34 mmol) and  $\text{Et}_3\text{N}$  (0.440 mL, 3.17 mmol) in 0.50 mL toluene according to the procedure described in Example **208C** to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min), 137 mg (0.400 mmol, 66%) of compound **224** as a white solid. HPLC: 100% at 2.73 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  401.0  $[\text{M}-\text{H}+\text{OAc}]$ .

15

**Example 225**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(Methylsulfinyl)-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile (225)**

20

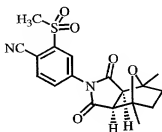


To an ice-cold suspension of compound **224** (30 mg, 0.088 mmol) in 2 mL of  $\text{H}_2\text{O}/\text{MeOH}$  (1:1) was added oxone (80 mg, 0.26 mmol) in one solid portion. The resulting mixture was stirred for 4 h at  $0^\circ\text{C}$  before it was

10 diluted with H<sub>2</sub>O (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL). The combined organic layers were dried and concentrated *in vacuo* to leave a residue which was purified by filtering the material through a short pad of silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub> to yield 32 mg (0.088 mmol, 100%) of  
 5 compound **225** as a colorless oil. HPLC: 99% at 2.01 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 376.0 [M+NH<sub>4</sub>]<sup>+</sup>.

### 10 Example 226

#### (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(Methylsulfonyl)-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile (**226**)



15

To a solution of compound **225** (48 mg, 0.14 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added *m*CPBA (145 mg, 50% mixture, 0.420 mmol) in one solid portion. The resulting mixture was allowed to warm to room temperature and was stirred for 60 h at which time no more starting material could be  
 20 detected by HPLC. The reaction was quenched by the addition of sat. NaHCO<sub>3</sub> solution (5 mL), the layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The combined organic phases were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The remaining residue was purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm  
 25 eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min) to afford 48 mg (0.13 mmol, 92%) of compound **226** as a white solid. HPLC: 100% at 2.07 min (retention time) (YMC S5 ODS

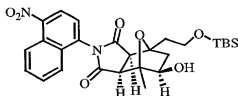
column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  392.0  $[M+NH_4]^+$ .

5

**Example 227****(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-7-[2-[(1,1-**

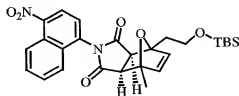
**Dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (227B)**

10

A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[2-[(1,1-

15

**Dimethylethyl)dimethylsilyl]oxy]ethyl]-3 $\alpha$ ,4,7,7 $\alpha$ -tetrahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (227A)**



20

A solution of compound **204A** (455 mg, 1.89 mmol) and 1-[4-nitronaphthalenyl]-1H-pyrrole-2,5-dione (254 mg, 0.947 mmol, prepared as described for 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile, Example 223A) in benzene (2 mL) was heated at 60°C overnight. The reaction mixture was concentrated under reduced pressure to give crude

compound **227A** as a brown solid, which was used directly in the next step without further purification.

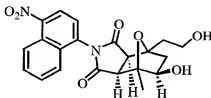
**B. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-7-[2-[(1,1-**

- 5 **Dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (227B)**

- 10  $\text{BH}_3 \cdot \text{THF}$  (0.95 mL, 0.95 mmol, 1M in THF) was added to a solution of crude compound **227A** (0.48 g, 0.95 mmol) in THF (2 mL) at 0°C. After compound **227A** was consumed, as was evident by HPLC, the reaction mixture was concentrated under reduced pressure. The resulting residue was then dissolved in toluene (2 mL),  $\text{Me}_3\text{NO}$  (71.0 mg, 2.84 mmol) was added and the mixture was heated to reflux overnight. The reaction
- 15 mixture was then cooled to rt, added to  $\text{H}_2\text{O}$  and extracted with EtOAc (3X). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash chromatography on  $\text{SiO}_2$  eluting with 75% EtOAc/hexanes, gave 130 mg (26%) of compound **227B** as a brown solid. HPLC: 94% at 3.92 min
- 20 (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  527.5  $[\text{M}+\text{H}]^+$ .

#### Example 228

- 25 **(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (228)**

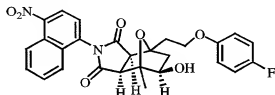


A mixture of TBAF (0.3 mL, 0.3 mmol, 1 M solution in THF) and HF (0.3 mL, 50% in H<sub>2</sub>O) in CH<sub>3</sub>CN (6 mL) was added to a solution of **227B** (104 mg, 0.197 mmol) in THF (2 mL) at 0°C. The reaction mixture was stirred overnight at rt. After the starting material was consumed, as was evident by TLC, H<sub>2</sub>O and EtOAc were added and the layers were separated. The aqueous layer was extracted with EtOAc (1X) and the combined organic layers were washed with H<sub>2</sub>O (1X) and brine (1X), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by flash chromatography on SiO<sub>2</sub> eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> gave 61 mg (75%) of compound **228** as a yellow solid. HPLC: 99% at 2.47 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 411.2 [M-H].

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Example 229

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-7-[2-(4-Fluorophenoxy)ethyl]hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (**229**)



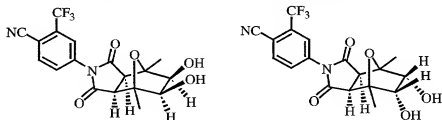
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DBAD (37.7 mg, 0.164 mmol) was added to a solution of PPh<sub>3</sub> (43.0 mg, 0.164 mmol) in THF (1 mL). After stirring for 10 min, 4-fluorophenol (18.3 mg, 0.164 mmol) was added and the reaction mixture was stirred for a further 5 min. A solution of compound **228** (45.0 mg, 0.109 mmol) in THF (1 mL) was added and the mixture was stirred at rt overnight. HPLC showed the crude reaction mixture to contain mostly starting diol (compound **228**), so this mixture was added to a preformed mixture as before of PPh<sub>3</sub> (86 mg), DBAD (75.4 mg) and phenol (36.6 mg) in THF (4

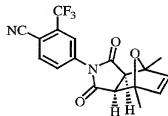
mL) at rt. Stirring was continued until all of compound **228** was consumed. The reaction was then concentrated under reduced pressure. Purification by reverse phase preparative HPLC [15.2 min (retention time) (YMC S5 ODS A column 20 x 100 mm, 10-90% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 25.0 mg (45%) of compound **229** as a light yellow solid. HPLC: 99% at 3.53 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 505.2 [M-H].

### Example 230

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (3 $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,6 $\alpha$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (230Bi & 230Bii, Respectively)



A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (230A)



2,5-Dimethyl furan (1.23 mL, 11.5 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (2.00 g, 7.69 mmol) were dissolved in benzene (10 mL) and heated at 60°C for 18 h. The volatile organics were then removed *in vacuo*. The resulting crude compound **230A** was carried on without purification. HPLC: 71% at 3.007 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

- 10 **B. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (3 $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,6 $\alpha$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (230Bi & 230Bii)**
- 15

Compound **230A** (0.100 g, 0.281 mmol) was dissolved in acetone and *N*-methylmorpholine-*N*-oxide (50% aq. solution, 0.10 mL, 0.42 mmol) was added. OsO<sub>4</sub> (4% aq. solution, 0.014 mmol) was then added. After 3 h at 25°C, the reaction was complete and sodium sulfite (0.250 g) was added with vigorous stirring. After 15 min, brine (10 mL) was added and the solution was extracted with EtOAc (3 x 15 mL). The organics were dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude diol mixture was purified by preparative TLC eluting with 18% acetone in chloroform to give 0.038 g (34%) of compound **230Bi** (beta face) and 0.012 g (11%) of compound **230Bii** (alpha face) as pale yellow solids. Compound **230Bi**: HPLC: 100% at 2.567 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 397.08 [M+H]<sup>+</sup>. Compound **230Bii**: HPLC: 100% at 2.417 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90%

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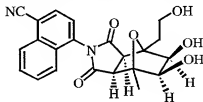
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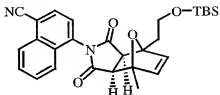
aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  397.08  $[M+H]^+$ .

### Example 231

- 5 (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-5,6-dihydroxy-4-(hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (231C)



- 10 A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (231A)



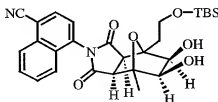
- 15 Compound **204A** (29.0 g, 120 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (20.0 g, 80.6 mmol) were suspended in benzene (80 mL) and heated at 60°C for 14 h. The mixture was then concentrated *in vacuo* at 40°C for 40 min. The resulting slurry was cooled to 25°C and then suspended in MeOH (200 mL) and stirred at rt for 30
- 20 min. The solution was then cooled to 0°C for 30 min and then filtered rinsing with cold MeOH. The resulting solid was dried *in vacuo* to give 26.1 g (55%) of crude compound **231A** as a white solid. The methanol solution was concentrated *in vacuo* and resuspended in MeOH (50 mL) and cooled to -20°C for 4 h. The solution was then filtered rinsing with
- 25 cold MeOH. The resulting solid was dried *in vacuo* to give 3.8 g (10%) of

compound **231A** as a white solid. HPLC: 95% at 4.227 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm)

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**B. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5,6-dihydroxy-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**231B**)**

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Compound **231A** (0.400 g, 0.851 mmol) was dissolved in acetone (9.0 mL) and *N*-methylmorpholine-*N*-oxide (50% aq. solution, 0.150 mL, 1.28 mmol) was added. OsO<sub>4</sub> (4% aq. solution, 0.043 mmol) was then added. After 3 h at 25°C, the reaction was complete and sodium sulfite (1.0 g) was added with vigorous stirring. After 15 minutes, brine (30 mL) was added and the solution extracted with EtOAc (3 x 50 mL). The organics were dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude diol was purified by flash chromatography on silica eluting with 5-25% acetone in chloroform to give 0.355 g (80%) of compound **231B** as a yellow solid. HPLC: 93% at 3.903 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 522.00 [M+H]<sup>+</sup>.

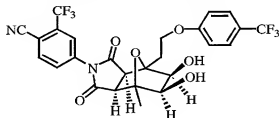
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**C. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-5,6-dihydroxy-4-(hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**231C**)**

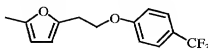
Compound **231B** (0.400 g, 0.766 mmol) was dissolved in THF (5.0 mL) and transferred to a polypropylene bottle and cooled to 0°C. HF•Pyridine (1.0 mL) was then added. After 20 min, the reaction was carefully poured into cold sat. aq. sodium bicarbonate and extracted with methylene chloride (3 x 30 mL). The organics were then washed once with 1 N HCl and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.290 g (93%) compound **231C** (0.290 g) as a yellow foam which was not purified further. HPLC: 92% at 2.273 and 2.423 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 409.10 [M+H]<sup>+</sup>.

#### Example 232

**(3α,4β,5β,6β,7β,7α)-4-[Octahydro-5,6-dihydroxy-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, (232C)**



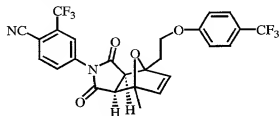
#### A. 2-Methyl-5-[2-[4-(trifluoromethyl)phenoxy]ethyl]furan (232A)



To a solution of triphenylphosphine (1.56 g, 5.95 mmol) in THF (40 mL) was added DBAD (1.37 g, 5.95 mmol). After 10 min, 4-

trifluoromethylphenol (0.964 g, 5.95 mmol) was added. After 10 additional minutes, compound **21A** (0.500 g, 3.97 mmol) was added. After 14 h at 25°C, the reaction was concentrated *in vacuo* and purified by flash chromatography on silica eluting with chloroform to give 0.713 g (44%) of compound **232A** as a clear oil.

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[1,3,3a,4,7,7a-hexahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (232B)**



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Compound **232A** (0.301 g, 1.15 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (0.220 g, 0.846 mmol) were suspended in benzene (1.5 mL) and heated at 60°C for 14 h. The mixture was then concentrated *in vacuo* at 40°C for 40 minutes. The crude product was purified by flash chromatography on silica eluting with 10 – 0% hexanes in methylene chloride to give 0.199 g (44%) of compound **232B** as a yellow solid. Compound **232B** was characterized as the *exo* diastereomer by NOE experiments. HPLC: 94% at 3.993 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

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**C. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-5,6-dihydroxy-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, (232C)**

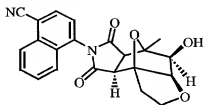
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- Compound **232B** (0.075 g, 0.14 mmol) was dissolved in acetone (2.0 mL) and *N*-methylmorpholine-*N*-oxide (50% aq. solution, 0.025 mL, 0.21 mmol) was added. OsO<sub>4</sub> (4% aq. solution, 0.007 mmol) was then added. After 3 h at 25°C, the reaction was complete and sodium sulfite (0.25 g) was added with vigorous stirring. After 15 minutes, brine (5 mL) was added and the solution extracted with EtOAc (3 x 10 mL). The organics were dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude diol was purified by preparative TLC on silica gel, eluting with 10% acetone in chloroform to give 0.038 g (48%) of compound **232C** as a yellow solid. HPLC: 98% at 3.747 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 593.08 [M+Na]<sup>+</sup>.

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**Example 233**

**(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,5 $\alpha$ ,8 $\alpha$ ,8 $\beta$ )-4-(Decahydro-5-hydroxy-4-methyl-1,3-dioxo-4,8a-epoxy-2H-furo[3,2-*c*]isoindol-2-yl)-1-naphthalenecarbonitrile, (233)**

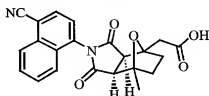


- To a solution of triphenylphosphine (0.072 g, 0.28 mmol) in THF (3.0 mL) was added DBAD (0.063 g, 0.28 mmol). After 10 min, 4-cyanophenol (0.033 g, 0.28 mmol) was added. After 10 additional minutes, compound **231C** (0.075 g, 0.18 mmol) was added. After 3 h at 25°C, the reaction was concentrated *in vacuo* and purified by preparative TLC on silica gel, eluting with 15% acetone in chloroform to give 0.068 g (95%) of compound **233** as a white solid. HPLC: 95% at 2.430 and 2.560 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90%

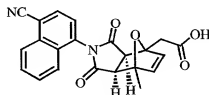
aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  391.09  $[M+H]^+$ .

### Example 234

5 **(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetic acid, (234B)**



10 **A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)-1,2,3,3a,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetic acid (234A)**



5-Methyl-2-furanacetic acid (0.500 g, 3.57 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (0.899 g, 3.57 mmol) were dissolved in benzene (3.0 mL) and heated at 60°C for 2 h and then cooled to 25°C. After 12 h, a white solid precipitated out of solution which was collected and rinsed with diethyl ether to yield 1.20 g (87%) of compound **234A** as a light yellow solid. NMR analysis showed only one diastereomer. HPLC: 86% at 2.767 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  389.45  $[M+H]^+$ .

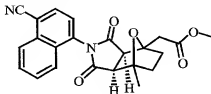
25 **B (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetic acid, (234B)**

Compound **234A** (1.10 g, 2.82 mmol) was dissolved in EtOH/EtOAc (1:1, 50 mL) and 10% Pd/C (0.4 g, cat.) was added. H<sub>2</sub> was introduced via a balloon. After 5 h at 25°C, the reaction was filtered through Celite rinsing with EtOAc and concentrated *in vacuo* to yield 1.00 g (91%) of compound **234B** as a yellow solid. HPLC: 80% at 2.84 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 391.1 [M+H]<sup>+</sup>.

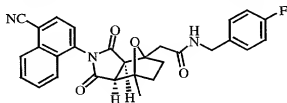
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**Example 235**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetic acid, methyl ester, (235)**



Compound **234B** (0.050 g, 0.13 mmol) was dissolved in acetonitrile (2.0 mL), then DCC (0.025 g, 0.13 mmol) was added followed by HOAc (0.018 g, 0.13 mmol). 4-Fluorobenzyl alcohol (0.014 mL, 0.13 mmol) was then added and the reaction was stirred for 3 h. The reaction mixture was concentrated *in vacuo* and purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm, 10-90% aqueous methanol over 15 min containing 0.1% TFA, 20 mL/min, monitoring at 220 nm). Purification yielded 0.040 g (82%) of compound **235** as a white solid, rather than the expected benzyl ester. None of the anticipated benzyl ester was observed by NMR or LC-MS. HPLC: 100% at 3.033 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 405.51 [M+H]<sup>+</sup>.

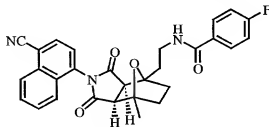
**Example 236****(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)-N-[(4-fluorophenyl)methyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetamide, (236)**

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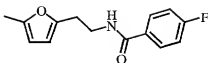
Compound **234B** (0.10 g, 0.27 mmol) was dissolved in acetonitrile (4.0 mL). HOAc (0.035 g, 0.27 mmol) and DCC (0.049 g, 0.27 mmol) were then added followed by 4-fluorobenzylamine (0.030 mL, 0.27 mmol). After 4 h at 25°C, the reaction was concentrated *in vacuo* and purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm, 10-90% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to yield 0.085 g (67%) of compound **236** as a white solid. HPLC: 100% at 3.277 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 498.43 [M+H]<sup>+</sup>.

**Example 237**  
**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-N-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]-4-fluorobenzamide, (237B)**

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**A. 4-Fluoro-N-[2-(5-methyl-2-furanyl)ethyl]benzamide (237A)**





4-Fluorophenylacetyl chloride (0.290 mL, 2.44 mmol) was added dropwise to a solution of  $\beta$ -(5-methyl-2-furanyl)ethanamine (300 mg, 2.44 mmol, made according to the procedure of Yur'ev et al. *J. Gen. Chem. USSR (Engl. Transl.)* 33, 3444-8 (1963)) in THF (2.5 mL) at rt, followed by the dropwise addition of Et<sub>3</sub>N (0.340 mL, 2.44 mmol). Once the starting material was consumed, as was evident by HPLC, the reaction was quenched with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with a gradient of 0-50% EtOAc/hexane gave 523 mg (95%) of compound **237A** as a white solid. HPLC: 99% at 2.84 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 248.15 [M+H]<sup>+</sup>.

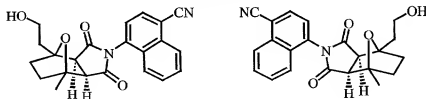
**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-N-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]-4-fluorobenzamide, (237B)**

A solution of compound **237A** (221 mg, 0.896 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (222 mg, 0.896 mmol) in benzene (4 mL) was heated at 60°C overnight. The reaction mixture was concentrated under reduced pressure and dissolved in EtOAc (30 mL). 10% Pd/C (50 mg) was added and the mixture was stirred under a hydrogen balloon overnight. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 25%-75% EtOAc/hexane (gradient) gave 160 mg (36%) of compound **237B** as an off-white solid. HPLC: 97% at 3.13 & 3.23 min (atropisomers, retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes

containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  498.11  $[M+H]^+$ .

### Example 238

- 5 [3aR-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aS-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile. (238i & 238ii)

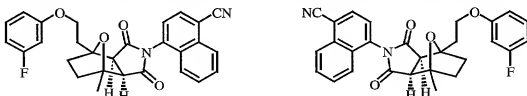


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- Racemic compound **223B** was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK AD 5 x 50 cm column; eluting with 20% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min, monitoring at 220 nm) to give the faster eluting compound **238i** (Chiral HPLC: 13.54 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting compound **238ii** (Chiral HPLC: 14.99 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). The absolute conformation for compounds **238i** & **238ii** was not established. For simplicity in nomenclature, compound **238i** is designated herein as having an "R" configuration and compound **238ii** as having an "S" configuration. Enantiomerically pure products derived from compound **238i** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **238ii** are designated herein as having an "S" configuration.
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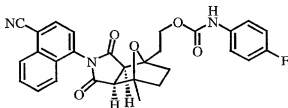
Example 239

[3aR-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aS-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (239i & 239ii)



- To a solution of triphenylphosphine (0.052 g, 0.20 mmol) in THF (2.0 mL) was added DBAD (0.046 g, 0.20 mmol). After 10 min, 3-fluorophenol (0.018 mL, 0.20 mmol) was added. After 10 additional minutes, compound **238i** (0.050 g, 0.13 mmol) was added. After 3 h at 25°C, the reaction was concentrated *in vacuo* and purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm, 10-90% aqueous methanol over 15 minutes containing 0.2% TFA, 20 mL/min, monitoring at 220 nm) to give 0.031 g (33%) of compound **239i** as a white solid. This process was repeated with compound **238ii** to yield compound **239ii**. Compound **239i**: HPLC: 100% at 3.80 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  471.65  $[M+H]^+$ ,  $[\alpha]_D^{25} = -47.371$  ( $c = 4.412$  mg/cc,  $CH_2Cl_2$ ). Compound **239ii**: HPLC: 100% at 3.80 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  471.65  $[M+H]^+$ ,  $[\alpha]_D^{25} = +24.3$  ( $c = 4.165$  mg/cc,  $CH_2Cl_2$ ).

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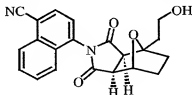
**Example 240****(4-Fluorophenyl)carbamic acid, 2-[ (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl ester, (240)**

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Compound **223B** (0.100 g, 0.279 mmol) was dissolved in dichloroethane (3.0 mL) and 4-fluorophenylisocyanate (0.048 mL, 0.42 mmol) was added followed by heating to 60°C. After 2 h, the reaction was cooled to 25°C and diluted with methylene chloride. The mixture was washed once with sat. aq. sodium bicarbonate (20 mL) and then the organics were dried over anhydrous sodium sulfate. The crude material was purified by flash chromatography on silica gel eluting with 15% acetone in chloroform to give 0.098 g (68%) of compound **240** as a yellow foam. HPLC: 98% at 3.320 & 3.457 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  514.13  $[M+H]^+$ .

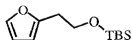
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**Example 241****(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (241D)**

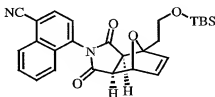
A. 2-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]furan (241A)

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2-(2-Hydroxyethyl)furan (1.00 g, 8.93 mmol, Example **255A**) was dissolved in DMF at 25°C and imidazole (0.790 g, 11.6 mmol) was added. TBSCl (1.35 g, 8.93 mmol) was then added in portions over 5 minutes. After 2 h, the reaction was poured into diethyl ether (300 mL) and washed sequentially with water (1 x 100 mL), 1 N HCl (1 x 100 mL), and brine (1 x 100 mL). The combined organics were then dried over magnesium sulfate and concentrated *in vacuo*. Compound **241A** was isolated as a clear oil (1.77 g) and was taken on without purification. HPLC: 100% at 4.233 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**241B**)**

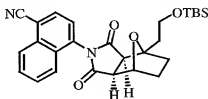


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4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (0.721 g, 3.40 mmol) was suspended in benzene (5.0 mL) in a sealed tube and compound **241A** (1.00 g, 4.42 mmol) was added. The reaction was heated at 60°C for 16 h and then cooled to 25°C. The benzene was removed *in vacuo* to give a yellow solid. The crude material was purified by flash chromatography on silica gel eluting with 1-5% acetone in chloroform to

give 1.37 g (85%) of compound **241B** as a yellow solid. NMR experiments confirmed the exo isomer assignment. HPLC: 100% at 4.030 & 4.110 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**241C**)**



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Compound **241B** (0.500 g, 1.14 mmol) was dissolved in ethyl acetate (40 mL) and 10% Pd/C (0.200 g) was added. Hydrogen was then introduced via a balloon. After 4 h, the reaction was filtered through Celite, rinsed with ethyl acetate and concentrated *in vacuo* to yield a pale yellow solid, which was purified by flash chromatography on silica gel eluting with acetone/chloroform (0% - 1.5% - 3% acetone) to give 0.450 g (83%) of compound **241C** as a yellow foam.

**D. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (**241D**)**

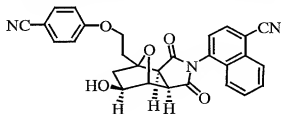
Compound **241C** (0.283 g, 0.594 mmol) was dissolved in a solution of 2% conc. HCl in absolute ethanol (10 mL). After 1 h, the reaction was quenched with sat. aq. sodium bicarbonate and extracted with methylene chloride (4 x 20 mL). The combined organics were dried over sodium sulfate and concentrated *in vacuo* to give 0.211 g (98%) of compound **241D**.

as a white solid. HPLC: 100% at 2.14 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  363.45  $[M+H]^+$ .

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**Example 242**

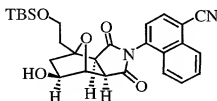
**(3 $\alpha$ ,4 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-6-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (242C)**



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- A. (3 $\alpha$ ,4 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-6-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (242A)**

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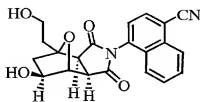


- Compound **241B** (1.00 g, 2.28 mmol) and Wilkinson's catalyst (0.105 g, 0.114 mmol) were stirred rapidly under vacuum at 25°C for 1 h and then purged with  $N_2$ . THF (30 mL) was then added followed by catecholborane (0.487 mL, 4.57 mmol) after the olefin was completely dissolved. After 1 h, the reaction was cooled to 0°C and a pH 7.2 phosphate buffer (33 mL) was added followed by EtOH (13 mL) and  $H_2O_2$  (30% aq. soln, 3.0 g). After 3 h at 0°C the reaction was complete by LC

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and the mixture was extracted with methylene chloride (3 x 50 mL). The combined organics were washed with a 1:1 mixture of 10% sodium sulfite/1 N NaOH (50 mL) and once with brine (50 mL). All aqueous phases were combined and extracted with methylene chloride (50 mL) and the organic phase combined with the previous extractions. All the organics were then dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 10-20% acetone in chloroform to give 0.634 g of compound **242A** as a white foam. HPLC: 96% at 3.797 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  493.13  $[M+H]^+$ .

**B. (3 $\alpha$ ,4 $\beta$ ,6 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-6-hydroxy-4-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**242B**)**



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Compound **242A** (0.400 g, 0.813 mmol) was dissolved in a solution of 2% 12 N HCl in absolute ethanol (10 mL). After 1 h, the reaction was quenched with sat. aq. sodium bicarbonate and extracted with EtOAc (4 x 20 mL). The combined organics were dried over sodium sulfate and concentrated *in vacuo* to give 0.305 g of compound **242B** as a white solid. HPLC: 90% at 2.043 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2%



phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  379.09  $[M+H]^+$ .

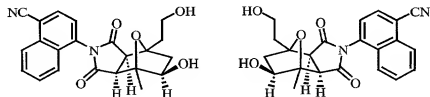
- C. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-  
6-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-  
naphthalenecarbonitrile, (242C)

To a solution of triphenylphosphine (0.054 g, 0.207 mmol) in THF (2.0 mL) was added DBAD (0.048 g, 0.207 mmol). After 10 min, 4-cyanophenol (0.025 g, 0.207 mmol) was added. After 10 additional minutes, compound **242B** (0.050 g, 0.138 mmol) was added. After 3 h at 25°C, the reaction was concentrated *in vacuo* and purified by preparative TLC on silica eluting with 25% acetone/chloroform to give 0.056 g of compound **242C** as a white solid. HPLC: 90% at 2.987 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  480.10  $[M+H]^+$ .

#### Example 243

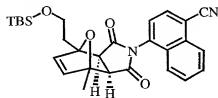
- 20 [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (243Di & 243Dii)

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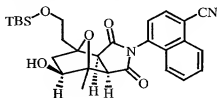
- A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-

**hexahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (243A)**



4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (18.3 g, 68.7 mmol) was added to a solution of compound **204A** (26.6 g, 110.6 mmol) in benzene (75 mL) and heated at 60°C overnight. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was treated with MeOH (250 mL) with stirring at 0°C for 10 min. The resulting solid was filtered, washed with cold MeOH (2 X 10 mL) and dried to give 26.7 g (79.5%) of compound **243A** as a yellow solid. HPLC analysis of the above solid revealed it to be 95% pure (HPLC conditions: 95% at 2.48 min (retention time) (Phenomenex-prime S5-C18 column, 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm)). The filtrate was then concentrated under reduced pressure and the resulting solid was chromatographed, eluting with 3% acetone/CHCl<sub>3</sub>, to give an additional 4.36 g of compound **243A** (13%), giving a total final yield of 92.5%.

**B. (3α,4β,5β,7β,7α)-4-[7-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (243B)**



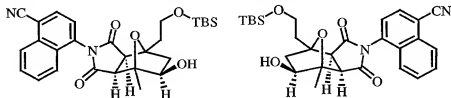
A mixture of **243A** (10 g, 20.46 mmol) and RhCl(PPh<sub>3</sub>)<sub>3</sub> (0.947 mg, 1.02 mmol) was evacuated and filled with argon (3X). THF (200 mL) was

added and once all particulates had dissolved, catecholborane (4.4 mL, 40.93 mmol) was slowly added dropwise. When the formation of product ceased, as was determined by HPLC, the reaction mixture was cooled to 0°C and quenched with phosphate buffer (330 mL, pH 7.2) then EtOH (130 mL) and H<sub>2</sub>O<sub>2</sub> (300 mL, 30% aq. sol) were added. Once boronate was consumed, the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X) and the combined organic layers were washed with 1 N NaOH, 10% aq. NaHSO<sub>5</sub> (1:1, 1X) and brine (1X). The combined washes was extracted with CH<sub>2</sub>Cl<sub>2</sub> (1X) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by flash chromatography on silica gel eluting with 10% to 30% acetone/CHCl<sub>3</sub> gradient over 25 min gave 7.1 g (68%) of **243B** as a light yellow solid. HPLC conditions: 98% at 3.82 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm).

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C. [3a*R*-(3α,4β,5β,7β,7α)]-4-[7-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3a*S*-(3α,4β,5β,7β,7α)]-4-[7-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**243Ci** & **243Cii**)

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The racemic compound **243B** was separated into the individual enantiomers by chiral normal phase liquid chromatography. A Chiralpak OD column (50 x 500 mm) was used, eluting with 13% EtOH/hexanes over 99 min at 50mL/min detecting at 220 nm. The faster eluting isomer

compound **243Ci** had a retention time = 45 min and the slower eluting isomer compound **243Cii** had a retention time = 66 min.

- D. [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (**243Di** & **243Dii**)

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Compound **243Ci** (0.84 g, 2.14 mmol) was dissolved in 2% 12 N HCl/EtOH (20 mL), stirred for 5 minutes and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 5-10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> gave 0.57 g (88%) of **243Di**. Compound **243Di** which came from the faster eluting isomer (**243Ci**) was found to be 99.7% ee by analytical normal phase chiral chromatography. HPLC conditions: 99.7% at 2.17 min (retention time) (Chiralcel OJ 44.6 X 250 mm, 10 micron, 40°C, isocratic 80% Heptane / 20% EtOH/MeOH (1:1), 1.0 mL/min., detection at 288 nm).

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Compound **243Cii** (0.86 g, 2.19 mmol) was dissolved in 2% 12 N HCl/EtOH (20 mL), stirred for 5 minutes and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 5-10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> gave 0.60 g (90%) of **243Dii**. Compound **243Dii** which came from the slower eluting isomer (**243Cii**) was found to have 87.1% ee by analytical chiral phase chromatography. HPLC conditions: 87.1% at 18.4 min (retention time) (Chiralcel OJ 44.6 X 250 mm, 10 micron, 40°C, isocratic 80% heptane / 20% EtOH/MeOH (1:1), 1.0 mL/min., detection at 288 nm).

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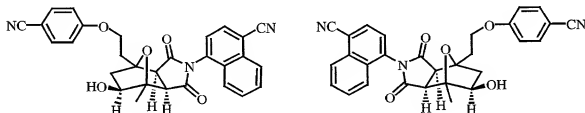
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The absolute conformation for compounds **243Di** & **243Dii** was not determined. For simplicity in nomenclature, compound **243Di** is designated herein as having an "S" configuration and compound **243Dii** as

having an "R" configuration. Enantiomerically pure products derived from compound **243Di** are designated herein as having an "S" configuration and enantiomerically pure products derived from compound **243Dii** are designated herein as having an "R" configuration

**Example 244**

**[3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (244i & 244ii)**



- 10 DBAD (26 mg, 0.115 mmol) was added to a solution of  $\text{PPh}_3$  (30 mg, 0.115 mmol) in THF (0.65 mL). After stirring for 10 min, 4-cyanophenol (13.6 mg, 0.115 mmol) was added and the reaction mixture was stirred for a further 5 min. Compound **243Di** (30 mg, 0.076 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 30% acetone/70%  $\text{CHCl}_3$  gave 23.1 mg (0.047 mmol, 61.7%) of compound **244i**. HPLC conditions: 95% at 3.06 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2%  $\text{H}_3\text{PO}_4$ , detecting at 220 nm). MS (ES):  $m/z$  494.09  $[\text{M}+\text{H}]^+$ .  $[\alpha]_D^{25} = 53.30^\circ$ ,  $C = 4.5 \text{ mg/cc}$  in THF, @ 589 nm)
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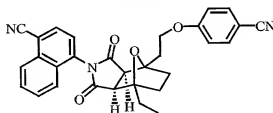
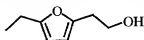
- DBAD (26 mg, 0.115 mmol) was added to a solution of  $\text{PPh}_3$  (30 mg, 0.115 mmol) in THF (0.65 mL). After stirring for 10 min, 4-cyanophenol (13.6 mg, 0.115 mmol) was added and the reaction mixture was stirred for a further 5 min. Compound **243Dii** (30 mg, 0.076 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 30% acetone/70%  $\text{CHCl}_3$  gave 20.3 mg (0.041 mmol, 54.2%) of compound **244ii**. HPLC conditions: 90% at 3.07 min (retention time)
- 25

(YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2%  $\text{H}_3\text{PO}_4$ , detecting at 220 nm). MS (ES):  $m/z$  494.09  $[\text{M}+\text{H}]^+$ .  $[\alpha]_D = -42.87^\circ$ ,  $C = 6.6$  mg/cc in THF, @ 589 nm)

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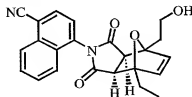
**Example 245**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.**

**(245D)****10 A. 2-Ethyl-5-(2-hydroxyethyl)furan (245A)**

$n$ -BuLi (2.5 M in hexane, 4.4 mL, 11 mmol) was added to a solution of 2-ethylfuran (1.05 mL, 10 mmol) in THF (10 mL) at  $-25^\circ\text{C}$ . The solution was warmed to rt and stirred for 3 h. Ethylene oxide (0.75 mL) was added at  $-78^\circ\text{C}$ . The reaction was stirred for 0.5 h at  $-15^\circ\text{C}$  and overnight at rt. Aqueous sat.  $\text{NH}_4\text{Cl}$  was added and the mixture was extracted with ether (3X). The combined extracts were washed with water (1X) and brine (1X) and dried over  $\text{Na}_2\text{SO}_4$ . Purification by flash chromatography on silica gel eluting with 30% EtOAc/70% hexane gave 1.12 g (8.02 mmol, 80.2%) of compound **245A** as a yellow oil.

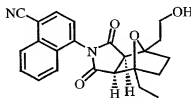
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**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-Ethyl-1,3,3a,4,7,7a-hexahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (245B)**

A solution of compound **245A** (280 mg, 2.00 mmol) and the 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (496 mg, 2.00 mmol) in benzene (2 mL) was stirred at 60°C for 2 h. The reaction mixture was concentrated under reduced pressure. The yellow solid, compound **245B**,  
 5 was used directly in the next step.

**C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**245C**)**

10



A mixture of compound **245B** (764 mg, 1.97 mmol) and 10% Pd/C (115 mg, cat.) in EtOAc (36 mL) was stirred under a hydrogen atmosphere at rt for 2 h. The reaction mixture was filtered through Celite and  
 15 concentrated under reduced pressure to give 779 mg of crude compound **245C**. Purification of this crude product by flash chromatography on silica gel eluting with 70% EtOAc/30% hexane gave 235 mg (0.6 mmol, 30.1%) of compound **245C**. HPLC conditions: 99% at 2.84 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute  
 20 gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm). MS (ES): m/z 391.12 [M+H]<sup>+</sup>.

**D. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**245D**)**

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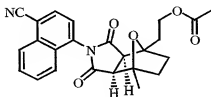
DBAD (44.2 mg, 0.192 mmol) was added to a solution of PPh<sub>3</sub> (50.4 mg, 0.192 mmol) in THF (1 mL). After stirring for 10 min, 4-cyanophenol



(23 mg, 0.192 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound **245C** (50 mg, 0.128 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/60% hexane gave 43 mg (0.087 mmol, 68.4%) of compound **245D** as a white solid. HPLC conditions: 99% at 3.65 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2%  $\text{H}_3\text{PO}_4$ , detecting at 220 nm). MS (ES):  $m/z$  492.16  $[\text{M}+\text{H}]^+$ .

#### Example 246

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[2-(Acetyloxy)ethyl]-2-(4-cyano-1-naphthalenyl)hexahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (246)**

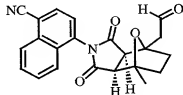


Compound **223B** (0.100 g, 0.279 mmol) was dissolved in methylene chloride (3.0 mL) at 25°C and pyridine (0.071 mL, 0.837 mmol) and 4-DMAP (1.0 mg) were added. Acetic anhydride (0.053 mL, 0.559 mmol) was then added and the reaction was stirred for 20 h at 25°C. After 20 h, sat. aq. sodium bicarbonate was added and the reaction was stirred for 30 min. The mixture was then extracted with methylene chloride (2 x 20 mL). The organics were then washed once with 1 N HCl (10 mL) and then dried over anhydrous sodium sulfate. After concentration *in vacuo*, the crude material was purified by preparative TLC on silica eluting with 12% acetone in chloroform to give 0.073 g of compound **246** as a yellow foam. HPLC: 95% at 2.837 and 3.027 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes

containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  441.10  $[M+Na]^+$ .

#### Example 247

- 5 (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-methyl-1,3-dioxo-7-(2-oxoethyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (247)



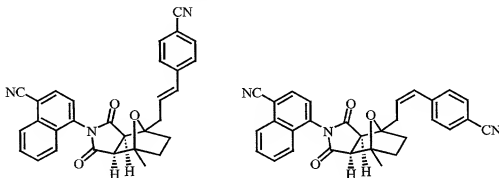
- Oxalyl chloride (2.0 M soln, 1.73 mL, 3.5 mmol) was added to dry  
 10 methylene chloride (10 mL) and cooled to  $-78^{\circ}\text{C}$ . DMSO (0.283 mL, 3.99 mmol) was then added dropwise with the evolution of gas. After 15 min, compound **223B** (1.00 g, 2.66 mmol) was then added in methylene chloride (10 mL). After 15 min, TEA (1.10 mL, 7.98 mmol) was added and the reaction was slowly warmed to  $25^{\circ}\text{C}$ . Water (30 mL) was then added and  
 15 the mixture was diluted with methylene chloride (100 mL). The organics were then washed once with 1 N HCl (30 mL), once with water (30 mL) and once with brine (30 mL) and then dried over anhydrous sodium sulfate. The crude product was isolated by concentration *in vacuo* to yield compound **247** as an orange foam. Crude compound **247** was taken on  
 20 directly to the next reaction. HPLC: 100% at 2.70 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  483.65  $[M+H]^+$ .

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#### Example 248

- [3 $\alpha$ ,4 $\beta$ (E),7 $\beta$ ,7 $\alpha$ ]-4-[4-[3-(4-Cyanophenyl)-2-propenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3 $\alpha$ ,4 $\beta$ (Z),7 $\beta$ ,7 $\alpha$ ]-4-[4-[3-(4-

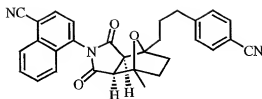
**Cyanophenyl)-2-propenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-  
2H-isoindol-2-yl]-1-naphthalenecarbonitrile (248i & 248ii)**



(4-cyanobenzyl)-triphenylphosphonium chloride (0.072 g, 0.174 mmol) was suspended in THF (2.0 mL) and cooled to 0°C. *n*-BuLi (1.6 M soln, 0.092 mL, 0.147 mmol) was then added dropwise resulting in a homogenous solution. The solution warmed to 25°C for 15 min and then cooled to 0°C. Compound **247** (0.050 g, 0.134 mmol) was then added in THF. After 1 h, the reaction was quenched with sat. aq. ammonium chloride and then extracted with methylene chloride (3 x 20 mL). The combined organics were dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude material was purified by preparative TLC eluting with 5% acetone in chloroform to give 0.010 g of a mixture of compounds **248i** & **248ii** as a white solid. A 1:1 mixture of E and Z olefin isomers characterized by NMR spectroscopy. HPLC: 100% at 3.517 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 474.2 [M+H]<sup>+</sup>.

**Example 249**

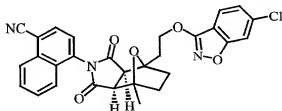
**(3α,4β,7β,7α)-4-[4-[3-(4-Cyanophenyl)propyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile,  
(249)**



The mixture of compounds **248i** & **248ii** (0.008 g, 0.017 mmol) was dissolved in EtOH (3.0 mL) and Pd/C (10% Pd, 0.008 g) was added. H<sub>2</sub> was then introduced via a balloon. After 18 h, the reaction was filtered through Celite, eluting with EtOAc, followed by concentration *in vacuo*. Compound **249** was isolated as a white solid (0.007 g). HPLC: 90% at 3.520 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 476.13 [M+H]<sup>+</sup>.

#### Example 250

#### (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(6-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile. (250)

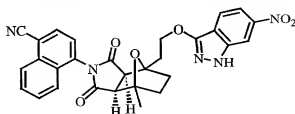


To a solution of PPh<sub>3</sub> (52 mg, 0.20 mmol) in 0.5 mL THF was added DBAD (46 mg, 0.20 mmol) as one solid portion. The resulting mixture was stirred for 10 min before 6-chloro-3-hydroxy-1,2-benzisoxazole (34 mg, 0.20 mmol) was added. Stirring was continued for 10 min before a solution of compound **223B** (50 mg, 0.13 mmol) in 0.5 mL THF was introduced via canula. The resulting mixture was stirred at ambient temperature for 24 h, concentrated *in vacuo* and purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm column; eluting with 30-100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed

- with sat.  $\text{NaHCO}_3$  solution, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to yield 50 mg (71%) of compound **250** as a colorless oil. HPLC: 3.89 min & 4.02 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2%  $\text{H}_3\text{PO}_4$ , 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  528.4  $[\text{M} + \text{H}]^+$ .

#### Example 251

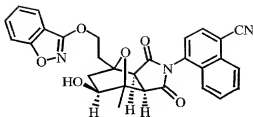
**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-methyl-7-[2-[(6-nitro-1H-indazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (251)**



- To a solution of compound **223B** (50 mg, 0.13 mmol) in toluene (1 mL) was added ADDP (50 mg, 0.20 mmol), 6-nitro-3-indazolinone (36 mg, 0.20 mmol) and *n*-Bu<sub>3</sub>P (50  $\mu\text{L}$ , 0.2 mmol). The resulting mixture was heated at 80°C for 24 h, concentrated *in vacuo* and purified by a combination of reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm column; eluting with 30-100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) and flash chromatography (silica gel, 25% acetone in  $\text{CHCl}_3$ ) to give 17 mg (25%) of compound **251** as a yellow solid. HPLC: 3.60 min & 3.74 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2%  $\text{H}_3\text{PO}_4$ , 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  537.6  $[\text{M} + \text{H}]^+$ .

#### Example 252

**[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-(1,2-Benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (252)**

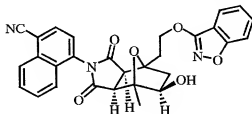


5  $\text{PPh}_3$  (47 mg, 0.18 mmol), DBAD (41 mg, 0.18 mmol), 3-hydroxy-1,2-benzisoxazole (24 mg, 0.18 mmol) and compound **243Di** (35 mg, 0.09 mmol) were reacted according to the procedure given for compound **250**. Purification was achieved by reverse phase HPLC (YMC S5 ODS 20 x 100 mm column; eluting with 30-100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in  $\text{CH}_2\text{Cl}_2$ , washed with sat.  $\text{NaHCO}_3$  solution, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to furnish 29 mg (64%) of compound **252** as a colorless oil. HPLC: 96% at 3.29 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 0-100% aqueous methanol over 4 minutes containing 0.2%  $\text{H}_3\text{PO}_4$ , 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  510.2  $[\text{M} + \text{H}]^+$ .

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#### Example 253

**[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (253)**



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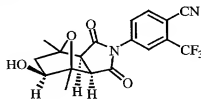
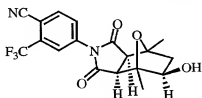
20  $\text{PPh}_3$  (47 mg, 0.18 mmol), DBAD (41 mg, 0.18 mmol), 3-hydroxy-1,2-benzisoxazole (24 mg, 0.18 mmol) and compound **243Dii** (35 mg, 0.09 mmol) were reacted according to the procedure given for compound **250**. Purification was achieved by reverse phase HPLC (YMC S5 ODS 20 x 100 mm column; eluting with 30-100% aqueous MeOH containing 0.1% TFA

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over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in  $\text{CH}_2\text{Cl}_2$ , washed with sat.  $\text{NaHCO}_3$  solution, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to furnish 23 mg (51%) of compound **253** as a colorless oil. HPLC: 95% at 3.29 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 0-100% aqueous methanol over 4 minutes containing 0.2%  $\text{H}_3\text{PO}_4$ , 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  510.4  $[\text{M} + \text{H}]^+$ .

#### Example 254

**[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile, (254i & 254ii)**

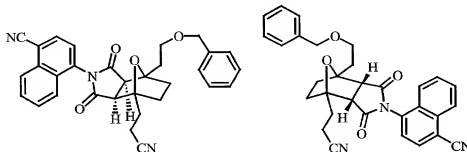


Racemic compound **221B** was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK AD 5 x 50 cm column; eluting with 20% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min) to give the faster eluting compound **254i** (Chiral HPLC: 10.02 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting **254ii** (Chiral HPLC: 14.74 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). (Names of title compounds based on absolute stereochemistry determination).

#### Example 255

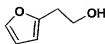
**(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile**

**& (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-**  
**7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-**  
**propanenitrile, (255Hi & 255Hii )**



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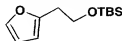
**A. 2-(2-Hydroxyethyl)furan (255A)**



2-(2-Hydroxyethyl)furan was made in accordance with the following reference: Harmata, M, et al. *J. Org. Chem.* 60, 5077-5092 (1995). *n*-BuLi (2.5 M in hexane, 44 mL, 110 mmol) was added to a solution of furan (8 mL, 110 mmol) in 100 mL of THF at  $-78^{\circ}\text{C}$ . The solution was stirred at  $0^{\circ}\text{C}$  for 4 h and then ethylene oxide (7.5 mL) was added at  $-78^{\circ}\text{C}$ . The reaction mixture was stirred at  $-15^{\circ}\text{C}$  for 1 h and then overnight at rt. The reaction was quenched with sat.  $\text{NH}_4\text{Cl}$  and extracted with ether (3X). The combined extracts were washed with water (1X) and brine (1X). The ether solution was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/60% hexane gave 5.4 g (48.2 mmol, 43.8%) of compound **255A** as a light brown oil.

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**B. 2-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]furan (255B)**



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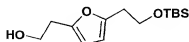
Imidazole (3.65 g, 53.6 mmol) and TBSCl (6.47 g, 42.9 mmol) were added to the solution of compound **255A** (4.00 g, 35.7 mmol) in 50 mL of DMF. The mixture was stirred at rt for 2 h and then the reaction mixture was poured into ether. The ether solution was washed with water (1X), 1 N HCl (1X), water (1X) and brine (1X). The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure.

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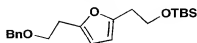
Purification by flash chromatography on silica gel eluting with 30%  $\text{CH}_2\text{Cl}_2$ /70% hexane gave 7.4 g (32.7 mmol, 91.7%) of **255B** as a colorless oil.

**C.**    **2-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-5-(2-hydroxyethyl)furan (255C)**



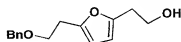
*t*-BuLi (1.2 M in pentane, 10 mL, 16.99 mmol) was added to a stirred solution of **255B** (3.49 g, 15.44 mmol) in 13 mL of THF at  $-78^\circ\text{C}$  dropwise. The mixture was stirred for an additional 4 h at  $0^\circ\text{C}$ . Ethylene oxide (1.05 mL) was added at  $-78^\circ\text{C}$  to the reaction solution. The mixture was warmed to rt and stirred overnight. Aqueous sat.  $\text{NH}_4\text{Cl}$  was added and most of the THF was removed under reduced pressure. The mixture was extracted with ether (3X) and the combined organic layers were washed with water (1X) and brine (1X) and dried over  $\text{Na}_2\text{SO}_4$ . Purification by flash chromatography on silica gel eluting with 5% EtOAc/95%  $\text{CH}_2\text{Cl}_2$  gave 2.8 g (10.4 mmol, 67%) of compound **255C** as a yellow oil.

**D.**    **2-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-5-[2-(phenylmethoxy)ethyl]furan (255D)**



The alcohol **255C** (1.00 g, 3.7 mmol) in 12 mL of THF was treated with 60% NaH (177.8 mg, 4.44 mmol), benzyl bromide (0.53 mL, 4.44 mmol) and tetrabutylammonium iodide (50 mg, 5%) for 3 h at rt. Water was added and the mixture was extracted with EtOAc (3X). The combined extracts were washed with water (1X) and brine (1X) and dried over  $\text{Na}_2\text{SO}_4$ . Purification by flash chromatography on silica gel eluting with 20% hexane/80%  $\text{CH}_2\text{Cl}_2$  gave 1.10 g (3.05 mmol, 82.6%) of compound **255D** as a yellow oil.

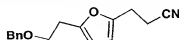
**E.**    **2-(2-Hydroxyethyl)-5-[2-(phenylmethoxy)ethyl]furan (255E)**



Tetrabutylammonium fluoride (1.0M in THF, 3.06 mL, 3.06 mmol) was added to the solution of compound **255D** (1.1 g, 3.06 mmol) in 10 mL of THF at 0°C. The reaction mixture was stirred at rt for 10 minutes, quenched by sat. NH<sub>4</sub>Cl and extracted with ether (3X). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>.

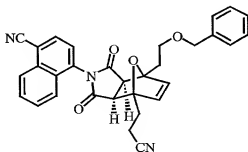
- 5 Purification by flash chromatography on silica gel eluting with 10% EtOAc/90% CH<sub>2</sub>Cl<sub>2</sub> gave 750 mg (3.05 mmol, 99.6%) of compound **255E** as a light yellow oil.

**F. 5-[2-(Phenylmethoxy)ethyl]furan-2-propanenitrile (255F)**



- 10 DEAD (1.285 mL, 8.17 mmol) was added to a stirred solution of Ph<sub>3</sub>P (2.14 g, 8.17 mmol) in 12 mL of dry THF at 0°C. The solution was stirred for 30 min at rt and compound **255E** (670 mg, 2.72 mmol) was added. The reaction was stirred for 15 min and acetone cyanohydrin (0.745 mL, 8.17 mmol) was added at -15°C. The reaction was stirred for 30 min at -15°C, then at rt overnight. The mixture was then
- 15 concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 100% CH<sub>2</sub>Cl<sub>2</sub> gave 180 mg (0.705 mmol, 26%) of compound **255F** as a colorless oil.

- G. (3α,4β,7β,7α)-2-(4-Cyano-1-naphthalenyl)-1,2,3,3a,7,7a-hexahydro-1,3-dioxo-7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile (255G)**
- 20



- A solution of compound **255F** (180 mg, 0.706 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (263 mg, 1.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was stirred at rt for 3 days. The reaction mixture was
- 25 concentrated under reduced pressure. Purification by flash

chromatography on silica gel eluting with 5% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> gave 318 mg (0.63 mmol, 89.6%) of compound **255G** as a light gray solid which was used directly in the next step.

5 **H. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-7-**

**[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile**

10 **& (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-**

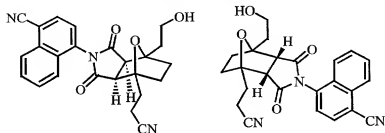
**7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile (255Hi & 255Hii)**

A mixture of compound **255G** (318 mg, 0.63 mmol) and 10% Pd/C (64 mg) in EtOH (10 mL) and EtOAc (5 mL) was stirred under a hydrogen atmosphere at rt overnight. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 320 mg of crude compounds **255Hi** & **255Hii**. Purification of 25 mg of this crude product by flash chromatography on silica gel eluting with 55% EtOAc/hexane gave 6.5 mg (0.013 mmol, 26% (based on 25 mg)) of compound **255Hi** & 8.1 mg (0.016 mmol, 32.4% (based on 25 mg)) of compound **255Hii**. Compound **255Hi**: HPLC conditions: 98% at 3.57 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm, MS (ES): m/z 506.15 [M+H]<sup>+</sup>. Compound **255Hii**: HPLC conditions: 98% at 3.51 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm). MS (ES): m/z 506.15 [M+H]<sup>+</sup>.

**Example 256**

30 **(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-4H-isoindole-4-propanenitrile &**

**(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-4H-isoindole-4-propanenitrile, (256i & 256ii)**

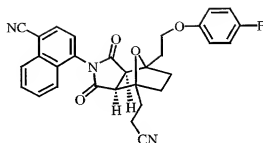


- 5 A mixture of compounds **255Hi** & **255Hii** (200 mg, 0.396 mmol) and PdCl<sub>2</sub> (8.4 mg, cat.) in EtOH (1 mL) and EtOAc (3 mL) was stirred under a hydrogen atmosphere (30 psi) at rt overnight. The reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> followed by a second column eluting with 100% EtOAc gave
- 10 28.9 mg (0.0696 mmol, 17.6%) of compound **256ii** and 26.5 mg (0.0639 mmol, 16.1%) of compound **256i**. Compound **256ii**: HPLC conditions: 90% at 2.44 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm.). MS (ES): m/z 416.11 [M+H]<sup>+</sup>. Compound **256i**: HPLC conditions: 99% at 2.47 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm). MS (ES): m/z 416.11 [M+H]<sup>+</sup>.

20

**Example 257**

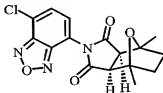
**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)-7-[2-(4-fluorophenoxy)ethyl]octahydro-1,3-dioxo-4,7-epoxy-4H-isoindole-4-propanenitrile. (257)**



DBAD (15 mg, 0.065 mmol) was added to a solution of PPh<sub>3</sub> (17 mg, 0.065 mmol) in THF (0.3 mL). After stirring for 10 min, 4-fluorophenol (7.33 mg, 0.065 mmol) was added and the reaction mixture was stirred for a further 5 min. Compound **256i** (18.1 mg, 0.044 mmol) was added and the mixture was stirred at rt for 3 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 60% EtOAc/30% hexane gave 5.9 mg (0.0116 mmol, 26.34%) of compound **257**. HPLC conditions: 98% at 3.59 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm). MS (ES): m/z 510.14 [M+H]<sup>+</sup>.

#### Example 258

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Chloro-2,1,3-benzoxadiazol-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (258)**



#### A. 4-Amino-7-chloro-2,1,3-benzoxadiazole (258A)



A solution of 1.0 g (5.02 mmol) of 4-chloro-7-nitrobenzofurazan in 20 mL AcOH, 10 mL EtOAc and 2 mL H<sub>2</sub>O was heated at 50°C and treated with iron powder (1.4 g, 251 mmol). The mixture was heated at 80°C for

30 min and then allowed to cool to rt. The mixture was filtered through Celite eluting with EtOAc. The filtrate was washed with sat. aq.  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure to give compound **258A** (0.80 g, 94%) as a red solid.

5

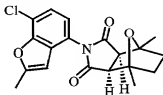
**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Chloro-2,1,3-benzoxadiazol-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (258B)**

- 10 Compound **258A** (42 mg, 0.25 mmol) was reacted in a sealed tube with compound **20A** (73.5 mg, 0.375 mmol),  $\text{MgSO}_4$  (75 mg, 0.625 mmol) and  $\text{Et}_3\text{N}$  (170  $\mu\text{L}$ , 1.25 mmol) in 250  $\mu\text{L}$  toluene according to the above procedure described in example **208C** to give after purification by reverse  
15 100% aqueous methanol containing 0.1% TFA over 12 min, 20 mL/min) 23 mg (26%) of compound **258B** as a yellow solid. HPLC: 97.6% at 2.87 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 minutes , 4 mL/min, monitoring at 220 nm). MS (DCI): m/z 347.9  $[\text{M}]^+$ .

20

**Example 259**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Chloro-2-methyl-4-benzofuran-5-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (259)**



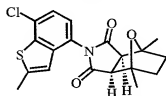
- 25 7-Chloro-2-methyl-4-benzofuranamine (38 mg, 0.25 mmol, prepared in accordance with the procedure described by Enomoto and Takemura in EP 0476697 A1) was reacted in a sealed tube with compound **20A** (73.5 mg, 0.375 mmol),  $\text{MgSO}_4$  (75 mg, 0.625 mmol) and  $\text{Et}_3\text{N}$  (170  $\mu\text{L}$ , 1.25 mmol) in 250  $\mu\text{L}$  toluene according to the procedure described in example

- 208C to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100 aqueous methanol containing 0.1% TFA over 12 min, 20 mL/min), 42 mg (47%) of compound **259** as a white solid. HPLC: 98% at 3.45 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (DCI):  $m/z$  359.9  $[M]^+$ .

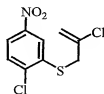
10

**Example 260**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Chloro-2-methylbenzo[b]thiophen-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione**

**(260)**

- 15 **A. 1-Chloro-2-(2-chloro-allylsulfanyl)-4-nitro-benzene (260A)**



- A solution of 2-chloro-5-nitro-benzenethiol (1.0 g, 5.27 mmol, prepared in accordance with the procedure described by Still et al. *Synth. Comm.* **13**, 1181 (1983)) in 15 mL DMF was treated with 2,3-dichloropropene (693  $\mu$ L, 7.52 mmol) and  $K_2CO_3$  (433 mg, 3.13 mmol). The mixture was heated at 80°C for 2 h and then allowed to cool to rt. EtOAc (200 mL) and  $H_2O$  (100 mL) were added. The organic phase was washed with  $H_2O$  (2 x 250 mL), saturated aqueous NaCl (100 mL), dried over  $MgSO_4$ , and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 20% EtOAc in hexanes to give compound **260A** (1.09 g, 89%) as an orange oil.

**B. 4-Amino-7-chloro-2-methylbenzo[b]thiophene (260B)**

- A solution of 1.09 g (4.67 mmol) of compound **260A** in 20 mL AcOH
- 5 with 10 mL EtOAc and 2 mL H<sub>2</sub>O was heated to 80°C and treated with iron powder (1.3 g, 23.4 mmol). The mixture was heated at 80°C for 40 min and then allowed to cool to rt. The mixture was filtered through Celite eluting with EtOAc. The filtrate was washed with sat. aq. NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. *N,N*-diethylaniline (10 mL) was added, and the reaction was heated at 215°C
- 10 for 6 h. After cooling to rt, 1 N aqueous HCl (20 mL) was added, and the reaction was stirred at room temperature for 2 h. The mixture was extracted with EtOAc (3 x 30 mL). The organic phase was washed with saturated aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*.
- 15 The crude material was purified by flash column chromatography on silica gel eluting with 25% EtOAc in hexanes to give compound **260B** (320 mg, 35%) as a beige solid.

**C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Chloro-2-methylbenzo[b]thiophen-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (260C)**

20

- Compound **260B** (49 mg, 0.25 mmol) was reacted in a sealed tube with compound **20A** (73.5 mg, 0.38 mmol), MgSO<sub>4</sub> (75 mg, 0.63 mmol) and
- 25 Et<sub>3</sub>N (170  $\mu$ L, 1.25 mmol) in 250  $\mu$ L toluene according to the procedure described in example **208C** to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 12 min containing 0.1% TFA, 20 mL/min), 28 mg

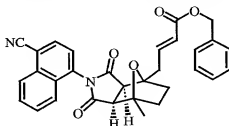


(30%) of compound **260C** as a pale yellow solid. HPLC: 96% at 3.18 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (DCI):  $m/z$  376.0  $[M]^+$ .

5

### Example 261

**(3 $\alpha$ ,4 $\beta$ (E),7 $\beta$ ,7 $\alpha$ )-4-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]-2-butenic acid, phenylmethyl ester, (261)**



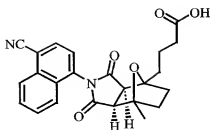
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Compound **247** (0.500 g, 1.34 mmol) was dissolved in THF (20 mL) and benzyl(triphenylphosphoranylidene) (0.55 g, 1.34 mmol) was added. The reaction mixture was stirred at 67°C for 2 h and then concentrated under reduced pressure. Purification by flash chromatography on  $\text{SiO}_2$  eluting with 5% acetone/95%  $\text{CHCl}_3$  gave 0.65 g of compound **261** as a yellow solid. HPLC: 99% at 3.717 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  507.1  $[M+H]^+$ .

20

### Example 262

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-butanolic acid, (262)**

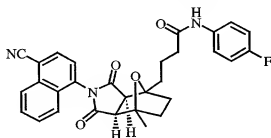


Compound **261** (0.60 g, 1.19 mmol) was dissolved in EtOH/EtOAc (5mL/5mL) and 10% Pd/C (0.30 g) was added. Hydrogen was then introduced via a balloon. After 8 h the reaction was filtered through  
 5 Celite and then concentrated under reduced pressure to give compound **262** (0.47 g) as a white solid. HPLC: 98% at 2.81 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  419.1  $[M+H]^+$ .

10

#### Example 263

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-2-(4-Cyano-1-naphthalenyl)-N-(4-fluorophenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-butanamide (263)**



15

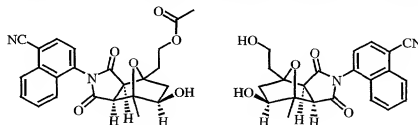
Compound **262** (0.030 g, 0.072 mmol) was dissolved in  $CH_3CN$  (1 mL). DCC (0.014 g, 0.072 mmol) and HOAc (0.0098 g, 0.072 mmol) were then added, followed by 4-fluoroaniline (0.007 mL, 0.072 mmol). The reaction mixture was stirred under argon for 14 h and the crude material  
 20 was dissolved in MeOH, purified by reverse phase preparative HPLC (YMC VP-ODS column, 20 x 100 mm, eluting with 20% B to 100% B in 15 minutes and hold @ 100%B for 10 minutes). Compound **263** (0.020 g) was isolated as white solid. HPLC: 100% at 3.217 min (retention time) (YMC

S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  512.1  $[M+H]^+$ .

5

**Example 264**

**[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-(Acetyloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (264 & 243Dii)**



10

A racemic mixture of compounds **243Di** & **243Dii** (1.90 gram) were dissolved in 100 mL of anhydrous THF in a 2 L flask. Anhydrous *tert*-butyl-methyl ether (900 mL) and vinyl acetate (40 mL) were transferred into the flask with stirring and lipase (20 g, typeII, crude, from porcine pancreas; Sigma, Cat# L3126) was added. The reaction mixture was stirred for 21 hr at rt at which point an additional 5 grams of the lipase and 20 mL of vinyl acetate were added. The reaction was stirred at rt for an additional 19 h, stored at 4°C without stirring for 36 h and then stirred at rt for another 22 h (until the desired % ee was apparent by chiral HPLC). To monitor the reaction, 200  $\mu$ L of the mixture was withdrawn and centrifuged. The supernatant (100  $\mu$ L) was dried under nitrogen and the resulting residue was dissolved in 100  $\mu$ L of EtOH and subjected to HPLC analysis:

- 25 1) Reverse phase HPLC: Column, YMC-ODS AQ 150x4.6; flow rate, 1.2 mL/min; sample size, 10  $\mu$ L

solvent A,: 1 mM HCl in water; solvent B, MeCN; monitored at 300 nm

Gradient:

Time(min) 0 8 8.5 9.5 10 12

5 B% 30 60 85 85 30 30

2) Chiral-HPLC: Column, CHIRALCEL OJ 4.6 x 250 mm  
mobile phase, hexanes/MeOH/EtOH (8:1:1)

flow rate, 1 mL/min; sample size, 20 uL

monitored at both 220 and 300 nm

10 performed at 25°C & 40°C.

(for ee% determination of reaction mixture)

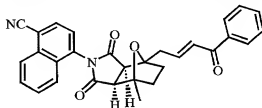
The enzyme was removed by filtration and filtrate was concentrated under reduced pressure. The resulting mixture was  
15 dissolved in  $\text{CHCl}_3$  and adsorbed onto silica gel (63-200 microns). These solids were applied to a VLC funnel (3 cm I.D., VLC is vacuum liquid chromatography using glass funnels having 24/40 joints at the bottom) containing a 5 cm bed height of silica gel (25-40 microns) and a step gradient was carried out. The gradient was 100%  $\text{CHCl}_3$  in the first 3  
20 fractions, followed by  $\text{CHCl}_3$ -1% MeOH (3 fractions),  $\text{CHCl}_3$ -2% MeOH (3 fractions),  $\text{CHCl}_3$ -3% MeOH (3 fractions),  $\text{CHCl}_3$ -4% MeOH (3 fractions), and finally with  $\text{CHCl}_3$ -5% MeOH (3 fractions). The volume of the fractions was 100 mL until reaching  $\text{CHCl}_3$ -3% MeOH and from that point on it was 200 mL. Compound **264** elutes in the last two fractions of  
25 100%  $\text{CHCl}_3$  and until the first fraction of  $\text{CHCl}_3$ -2% MeOH. Compound **243Dii** elutes starting with the second fraction of  $\text{CHCl}_3$ -2% MeOH, and continues to the first fraction of  $\text{CHCl}_3$ -5% MeOH. The crude compound **243Dii** contained a small amount of a colored impurity which was removed by a Sephadex column [LH-20 swollen in  $\text{CHCl}_3$ -MeOH (2:1),  
30 column (2.5 cm I.D. & 90 cm long) to yield 632 mg of compound **243Dii**. Compound **264**: HPLC conditions: 98% at 7.2 min (retention time)

(method 1), chiral HPLC conditions: 29.0 min @ 25°C (method 2).  
Compound **243Dii**: HPLC conditions: 98% at 4.6 min (retention time)  
(method 1), chiral HPLC conditions: 96% ee at 25.7 min (retention time)  
(@ 25°C) & 19.8 min (retention time) (@ 40°C) (method 2).

5

**Example 265**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ (E))-4-[Octahydro-4-methyl-1,3-dioxo-7-(4-oxo-4-phenyl-2-butenyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (265)**



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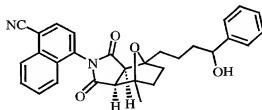
The compound **247** (0.050 g, 0.134 mmol) was dissolved in THF (1.5 mL) and (phenacylidene)triphenylphosphorane (0.051 g, 0.134 mmol) was added. The reaction mixture was stirred at 67°C for 24 h and then cooled to 23°C and concentrated *in vacuo*. The crude material was then purified by reverse phase preparative HPLC. (YMC VP-ODS column, 20 x 100 mm, eluting with 20% B to 100%B in 15 minutes and hold @ 100%B for 10 minutes.) to give compound **265** (0.040 g) as white solid. HPLC: 100% at 3.503 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 477.1 [M+H]<sup>+</sup>.

20

Example 266

(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ (E))-4-[Octahydro-4-methyl-1,3-dioxo-7-(4-hydroxy-4-phenyl-2-butyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (266)

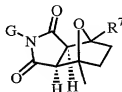
5



Compound **265** (0.010 g, 0.021 mmol) was dissolved in EtOH (2.0 mL) and Pd/C (10% Pd, 0.005 g) was added. Hydrogen was then introduced via a balloon and the reaction was stirred at 25°C for 3 h. The reaction was then filtered through Celite rinsing with EtOAc and concentrated *in vacuo* to give compound **266** as a tan solid (0.009 g). No purification was necessary. HPLC: 100% at 3.38 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  503.2  $[M+Na]^+$ . (Where this reaction was run for 1 hour, the resulting product was compound **455**.)

Examples 267 to 378

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 267 to 378 have the following structure (L is a bond):



25

where G, R<sup>7</sup>, the compound name, retention time, molecular mass, and the procedure employed, are set forth in **Table 5**. The absolute

- configuration for the following compounds was not determined. For simplicity in nomenclature, compound **238i** is designated herein as having an “R” configuration and compound **238ii** as having an “S” configuration. Enantiomerically pure products derived from compound **238i** are
- 5 designated herein as having an “R” configuration and enantiomerically pure products derived from compound **238ii** are designated herein as having an “S” configuration.


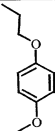

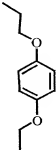
- The chromatography techniques used to determine the compound retention times of **Table 5** are as follows: **LCMS** = YMC S5 ODS column, 4.6 X 50 mm
- 10 eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LCMS\*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.
- 15 The molecular mass of the compounds listed in **Table 5** were determined by MS (ES) by the formula m/z.


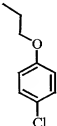

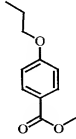


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
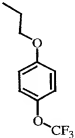


Table 5.


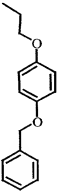


Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
267			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-[7-[2-(4-Bromophenoxy)ethyl]octahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.97 LCMS 549.0 [M+H] <sup>+</sup>	204, 35
268			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-[Octahydro-7-[2-(4-iodophenoxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	4.09 LCMS 597.0 [M+H] <sup>+</sup>	204, 35
269			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(4-	3.95 LC	204, 35




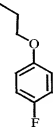

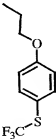

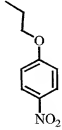
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.		
270			(3α,4β,7β,7aα)-4-[Octahydro-7-[2-(4-methoxyphenoxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.66 LC	204, 35
271			(3α,4β,7β,7aα)-4-[7-[2-(4-ethoxyphenoxy)ethyl]octahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.81 LC	204, 35


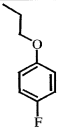


Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			(trifluoromethyl)benzonitrile.		
272			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-(4-Chlorophenoxy)ethyl]octahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]- (trifluoromethyl)benzonitrile.	3.97 LCMS 522.2 [M+H] <sup>+</sup>	204, 35
273			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxybenzoic acid, methyl ester.	3.77 LCMS 529.12 [M+H] <sup>+</sup>	204, 35
274			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- $\alpha$ -Hexahydro-4-(2-hydroxyethyl)	2.44 LC	204, 35




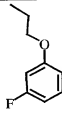

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
			-7-methyl-2-(3-methyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
275			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethoxy)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.97 LC	204, 35
276		CH <sub>3</sub>	(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-2-(3,5-Dichlorophenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.31 LCMS 341.2 [M+H] <sup>+</sup>	20
277		CH <sub>3</sub>	(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-Hexahydro-4,7-dimethyl-2-(4-nitro-1-	3.04 LCMS	20






Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
			naphthalenyl)- -4,7-epoxy- 1H-isindole- 1,3(2H)-dione.		
278			(3α,4β,7β,7a α)-4- [Octahydro-4- methyl-1,3- dioxo-7-[2-[4- (phenylmethoxy)phenoxy]ethyl]-4,7- epoxy-2H- isindol-2-yl]- 2- (trifluoromethyl)benzoxazole.	4.06 LC	204, 35
279			(3α,4β,7β,7a α)- Hexahydro-4- (2- hydroxyethyl)- -7-methyl-2- (4-nitro-1- naphthalenyl)- -4,7-epoxy- 1H-isindole- 1,3(2H)-dione.	2.607 & 2.743 rotational isomers LC	204, 35

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
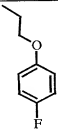

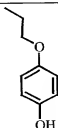
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
280			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ ) $\alpha$ -4-[2-(4-Fluorophenoxy)ethyl]hexahydro-7-methyl-2-(3-methyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.68 LC	204, 35
281			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ ) $\alpha$ -4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-[(trifluoromethyl)thio]phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	4.11 LC	204, 35
282			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ ) $\alpha$ -4-[Octahydro-4-methyl-7-[2-(4-nitrophenoxy)ethyl]-1,3-dioxo-4,7-	3.68 LC	204, 35


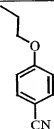

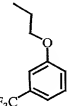

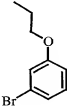
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			epoxy-2H-isindol-2-yl]-2-(trifluoromethyl)benzonitrile.		
283			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[2-(4-Fluorophenoxy)ethyl]hexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isindole-1,3(2H)-dione.	3.68 & 3.80 rotational isomers LC	204, 35
284			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-7-methyl-1,3-dioxo-7-[2-[2-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.89 LC	204, 35





Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
285			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-[4-[2-(2-Bromophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.91 LC	204, 35
286			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.78 LC	204, 35
287		H	(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-Hexahydro-2-[4-(1H-imidazol-1-yl)phenyl]-4-methyl-4,7-epoxy-1H-isoindole-	1.16 LC	3


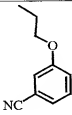

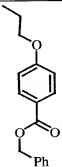
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			1,3(2H)-dione.		
288		H	(3α,4β,7β,7a α)-2-[3- Chloro-4-(2- thiazolyl)phe- nyl]hexahydr- o-4-methyl- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	2.81 LC	3
289		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro- 4,7-dimethyl- 2-(3-methyl-4- nitrophenyl)- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	2.74 LC	20
290		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro- 4,7-dimethyl- 2-(2-methyl-4- nitrophenyl)- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	2.71 LC	20
291			(3α,4β,7β,7a α)-2-(3,5- Dichlorophen- yl)hexahydro- 4-(2-	2.98 LC	204


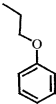




Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
			hydroxyethyl)- -7-methyl-4,7- epoxy-1H- isoindole- 1,3(2H)-dione.		
292			(3α,4β,7β,7a α)-2-(3,5- Dichlorophen yl)-4-[2-(4- fluorophenoxy ethyl)hexahy dro-7-methyl- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	4.03 LC	204, 35
293			(3α,4β,7β,7a α)-4- [Octahydro-4- [2-(4- hydroxypheno xy)ethyl]-7- methyl-1,3- dioxo-4,7- epoxy-2H- isoindol-2-yl]- 2- (trifluorometh yl)benzonitril e.	3.25 LC	204, 35



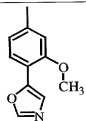
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
294			(3α,4β,7β,7a α)-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-(trifluoromethyl)benzonitrile.	3.51 LC	204, 35
295			(3α,4β,7β,7a α)-4-[4-[2-[3-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-(trifluoromethyl)benzonitrile.	3.85 LC	204, 35
296			(3α,4β,7β,7a α)-4-[4-[2-(3-Bromophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-	3.84 LC	204, 35


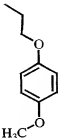

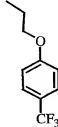

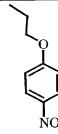
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min/</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
			isindol-2-yl]-2-(trifluoromethyl)benzonitrile.		
297			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-4-[4-(4-Fluorophenyl)methyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-(trifluoromethyl)benzonitrile.	3.73 LC	205
298		CH <sub>3</sub>	(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-2-(1,6-Dihydro-1-methyl-6-oxo-3-pyridinyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isindole-1,3(2H)-dione.	1.61 LC	20
299		CH <sub>3</sub>	(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-Hexahydro-4,7-dimethyl-	1.73 LC	20



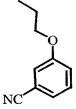

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
			2-(1-methyl-6-oxo-3-piperidinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
300			(3α,4β,7β,7aα)-4-[4-[2-(3-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.46 LC	204, 35
301			(3α,4β,7β,7aα)-4-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxybenzoic acid, phenylmethyl ester.	4.01 LC	204, 35

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
302			(3α,4β,7β,7a α)-4- [Octahydro-4- methyl-1,3- dioxo-7-(2- phenoxyethyl) -4,7-epoxy- 2H-isindol-2- yl]-2- (trifluorometh yl)benzonitril e.	3.57 LC	204, 35
303		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-(3,5- Dichloro-4- nitrophenyl)h exahydro-4,7- dimethyl-4,7- epoxy-1H- isindole- 1,3(2H)-dione.	3.40 LC	20
304		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-(3,5- Dichloro-4- hydroxypheny l)hexahydro- 4,7-dimethyl- 4,7-epoxy-1H- isindole- 1,3(2H)-dione.	2.58 LC	20

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


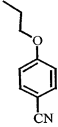

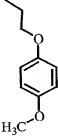
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
305		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-(5- Fluoro-1- naphthalenyl) hexahydro- 4,7-dimethyl- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	2.96 & 3.06 rotational isomers LC	20
306		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro- 4,7-dimethyl- 2-(1- naphthalenyl) -4,7-epoxy- 1H-isoindole- 1,3(2H)-dione.	2.60 & 2.73 rotational isomers LC	20
307		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro-2- [3-methoxy-4- (5- oxazolyl)phen yl]-4,7- dimethyl-4,7- epoxy-1H- isoindole- 1,3(2H)-dione.	2.62 LC	20


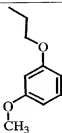

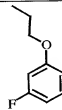
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
308			(3α,4β,7β,7a α)-Hexahydro-4-[2-(4-methoxyphenoxy)ethyl]-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.42 & 3.55 rotational isomers LC	204, 35
309			(3α,4β,7β,7a α)-Hexahydro-4-methyl-2-(4-nitro-1-naphthalenyl)-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.81 & 3.93 rotational isomers LC	204, 35
310			(3α,4β,7β,7a α)-Hexahydro-4-methyl-2-(4-nitro-1-naphthalenyl)-7-[2-(4-nitrophenoxy)	3.48 & 3.61 rotational isomers LC	204, 35

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of <u>Ex.</u>
			ethyl]-4,7- epoxy-1H- isoindole- 1,3(2H)-dione.		
311		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-(1,6- Dihydro-1,4- dimethyl-6- oxo-3- pyridinyl)hex ahydro-4,7- dimethyl-4,7- epoxy-1H- isoindole- 1,3(2H)-dione.	1.89 LC	20
312			(3α,4β,7β,7a α)-4- [Octahydro-7- methyl-2-(4- nitro-1- naphthalenyl)- 1,3-dioxo-4,7- epoxy-4H- isoindol-4- yl]ethoxy]ben zonitrile.	3.63 LC	204, 35
313		CH <sub>3</sub>	(3α,4β,7β,7a α)-4- (Octahydro- 4,7-dimethyl- 1,3-dioxo-4,7- epoxy-2H- isoindol-2-yl)-	2.38 LC	20


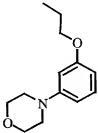

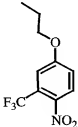

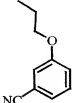
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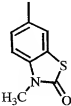
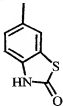

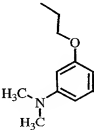



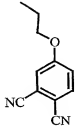
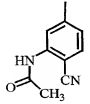

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			1,2-benzenedicarbonylnitrile.		
314			(3α,4β,7β,7aα)-4-(2-Bromoethyl)hexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.52 LC	36
315			(3α,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.19 & 3.35 rotational isomers LC	223, 35
316			(3α,4β,7β,7aα)-4-[2-(4-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-	3.34 & 3.50 rotational isomers LC	223, 35

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			isoindol-2-yl]- 1- naphthalenec arbonitrile.		
317			(3α,4β,7β,7a α)-4- [Octahydro-4- [2-(3- methoxyphen oxy)ethyl]-7- methyl-1,3- dioxo-4,7- epoxy-2H- isoindol-2-yl]- 1- naphthalenec arbonitrile.	3.34 & 3.50 rotational isomers LC	223, 35
318			(3α,4β,7β,7a α)-4-[4-[2-(3- Fluorophenox y)ethyl]octahy dro-7-methyl- 1,3-dioxo-4,7- epoxy-2H- isoindol-2-yl]- 1- naphthalenec arbonitrile.	3.46 & 3.61 rotational isomers LC	223, 35


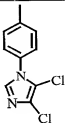
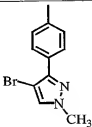
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



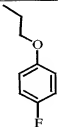
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
319			(3α,4β,7β,7a α)-4-[Octahydro-4-methyl-7-[2-[3-(4-morpholinyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.01 & 3.18 rotational isomers LC	223, 35
320			(3α,4β,7β,7a α)-4-[Octahydro-4-methyl-7-[2-[4-nitro-3-(trifluoromethyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.70 & 3.83 rotational isomers LC	223, 35
321			(3α,4β,7β,7a α)-4-[4-[2-(3-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-	3.39 & 3.55 rotational isomers LC	223, 35


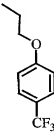

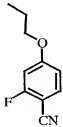
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			epoxy-2H-isoindol-2-yl]-1-naphthalene carbonitrile.		
322		CH <sub>3</sub>	(3α,4β,7β,7aα)-2-(2,3-Dihydro-3-methyl-2-oxo-6-benzothiazolyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.34 LC	20
323		CH <sub>3</sub>	(3α,4β,7β,7aα)-2-(2,3-Dihydro-2-oxo-6-benzothiazolyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.16 LC	20
324			(3α,4β,7β,7aα)-4-[4-[2-[3-(Dimethylamino)phenoxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-	2.63 & 2.79 rotational isomers LC	223, 35

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.		
325			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-[2-[4-Cyano-3-(trifluoromethyl)phenyl]phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy)-1,2-benzenedicarbonitrile.	3.42 LC	223, 35
326		CH <sub>3</sub>	(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-N-[2-Cyano-5-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)phenyl]acetamide.	1.94 LC	20
327		CH <sub>3</sub>	(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-(Octahydro-4,7-dimethyl-	3.52 LC	20


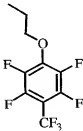
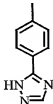
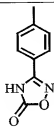
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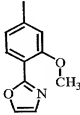


Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-(trifluoromethoxy)benzonitrile.		
328		CH <sub>3</sub>	(3α,4β,7β,7aα)-2-Methoxy-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile.	2.47 LC	20
329		CH <sub>3</sub>	(3α,4β,7β,7aα)-2-[4-(4,5-Dichloro-1H-imidazol-1-yl)phenyl]hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.09 LC	20
330		CH <sub>3</sub>	(3α,4β,7β,7aα)-2-[4-(4-Bromo-1-methyl-1H-pyrazol-3-yl)phenyl]hexahydro-4,7-	3.04 LC	20


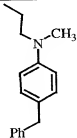


Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
			dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
331			(3α,4β,7β,7a α)-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	2.44 & 2.60 rotational isomers LC	223
332		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-Iodo-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzotrile.	2.78 LC	20
333			(3α,4β,7β,7a α)-4-[4-[2-(4-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-	3.39 & 3.53 rotational isomers LC	223, 35




Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			1-naphthalenecarbonitrile.		
334			(3α,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.66 & 3.78 rotational isomers LC	223, 35
335			(3α,4β,7β,7aα)-4-[4-[2-(4-Cyano-3-fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.26 & 3.41 rotational isomers LC	223, 35





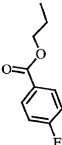

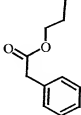
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
336			(3α,4β,7β,7a α)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.94 & 4.01 rotational isomers LC	223, 35
337		CH <sub>3</sub>	(3α,4β,7β,7a α)-Hexahydro-4,7-dimethyl-2-[4-(1H-1,2,4-triazol-3-yl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.06 LC	20
338		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-[4-(4,5-Dihydro-5-oxo-1,2,4-oxadiazol-3-yl)phenyl]hexahydro-4,7-dimethyl-4,7-	2.42 LC	20


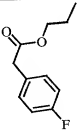

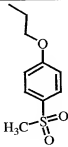
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			epoxy-1H- isoindole- 1,3(2H)-dione.		
339		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro-2- [3-methoxy-4- (2- oxazolyl)phen yl]-4,7- dimethyl-4,7- epoxy-1H- isoindole- 1,3(2H)-dione.	2.51 LC	20
340		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro-2- (4-hydroxy-1- naphthalenyl) -4,7-dimethyl- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	2.30 LC	20
341		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro-2- (8-hydroxy-5- quinolinyl)- 4,7-dimethyl- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione, trifluoroaceta	1.49 LC	20

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			te (1:1).		
342			(3α,4β,7β,7a α)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[methyl(phenylmethyl)amino]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	2.42 LC	204, 35
343		CH <sub>3</sub>	(3α,4β,7β,7a α)-Hexahydro-4,7-dimethyl-2-(5-quinoliny)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	1.69 LC	20
344		CH <sub>3</sub>	(3α,4β,7β,7a α)-5-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-pyridinecarbo	2.18 LC	20




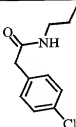
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			nitrile.		
345		CH <sub>3</sub>	(3α,4β,7β,7a α)-5-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-8-quinolinecarb onitrile.	2.31 LC	20
346		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-(5-Bromo-4-nitro-1-naphthalenyl) hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.10 & 3.29 rotational isomers LC	20
347		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-(5-Bromo-1-naphthalenyl) hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.28 & 3.40 rotational isomers LC	20


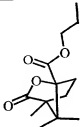

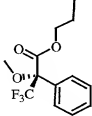
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Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
348		CH <sub>3</sub>	(3α,4β,7β,7a α)-Hexahydro-4,7-dimethyl-2-[8-(trifluoromethyl)-4-quinoliny]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.08 LC	20
349			4-Fluorobenzoic acid, 2-[(3α,4β,7β,7a α)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl ester.	3.64 & 3.77 rotational isomers LC	223
350			Benzeneacetic acid, 2-[(3α,4β,7β,7a α)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-	3.53 & 3.67 rotational isomers LC	223


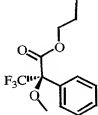


Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			epoxy-4H-isindol-4-ylethyl ester.		
351			4-Fluorobenzenecetic acid, 2-[ (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isindol-4-ylethyl ester.	3.53 & 3.66 rotational isomers LC	223
352			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- $\alpha$ -Hexahydro-4-methyl-7-[2-[4-(methylsulfonyl)phenoxy]ethyl]-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isindole-1,3(2H)-dione.	3.31 LC	204, 35

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
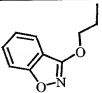



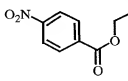
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
353		CH <sub>3</sub>	(3α,4β,7β,7a α- Hexahydro-2- (2- naphthalenyl) -4,7-dimethyl- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	2.94 LC	20
354		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-(4- Chloro-1- naphthalenyl) hexahydro- 4,7-dimethyl- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	3.22 & 3.34 rotational isomers LC	20
355			(3α,4β,7β,7a α)-N-[(4- Chlorophenyl) methyl]-2-(4- cyano-1- naphthalenyl) octahydro-7- methyl-1,3- dioxo-4,7- epoxy-4H- isoindole-4- acetamide.	3.52 LC	237


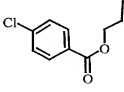

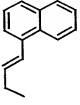
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
356			4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid, 2-[(3α,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-ylethyl ester.	3.45 LC	223
357			(αS)-α-Methoxy-α-(trifluoromethyl)benzeneacetic acid, 2-[(3α,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-ylethyl ester.	3.91 LC	223





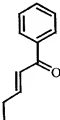

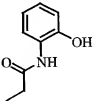
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
358			( $\alpha R$ )- $\alpha$ -Methoxy- $\alpha$ -(trifluoromethyl)benzeneacetic acid, 2-[[3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ ]-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl ester.	2.00 LC	223
359			(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )-4-[Octahydro-4-methyl-7-[2-[(7-methyl-1,2-benzisoxazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.79 & 3.92 LC Rotationale isomers	250

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
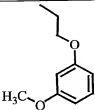

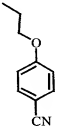

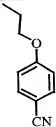

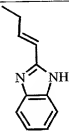
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
360			(3α,4β,7β,7a α)-4-[4-(2- (1,2- Benzisoxazol- 3- yloxy)ethyl]oc tahydro-7- methyl-1,3- dioxo-4,7- epoxy-2H- isoindol-2-yl]- 1- naphthalenec arbonitrile.	3.55 & 3.70 LC Rotationale Isomers	250
361			(3α,4β,7β,7a α)-4-[2- (Benzoyloxy)e thyl]-2-(4- cyano-1- naphthalenyl) hexahydro-7- methyl-4,7- epoxy-1H- isoindole- 1,3(2H)-dione.	3.51 & 3.66 LC Rotationale isomers	223
362			(3α,4β,7β,7a α)-2-(4- Cyano-1- naphthalenyl) -4-[2-(4- nitrobenzoyl)o xy]ethyl]hexa hydro-7-	3.52 & 3.67 LC Rotationale Isomers	223


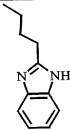
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			methyl-4,7- epoxy-1H- isoindole- 1,3(2H)-dione.		
363			4- Chlorobenzoic acid, 2- [(3α,4β,7β,7a α)-2-(4-cyano- 1- naphthalenyl) octahydro-7- methyl-1,3- dioxo-4,7- epoxy-4H- isoindol-4- ylethyl ester.	3.79 LC	223
364			[3α,4β,7β,7a α(E)]-4- [Octahydro-4- methyl-7-[3- (1- naphthalenyl) -2-propenyl]- 1,3-dioxo-4,7- epoxy-2H- isoindol-2-yl]- 1- naphthalenec arbonitrile.	4.14 LC 499.13 [M+H] <sup>+</sup>	248

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
365			(3α,4β,7β,7a α)-4- [Octahydro-4- methyl-7-[3- (1- naphthalenyl) propyl]-1,3- dioxo-4,7- epoxy-2H- isoindol-2-yl]- 1- naphthalene- carbonitrile.	4.14 LC 501.14 [M+H] <sup>+</sup>	248, 249
366		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro- 4,7-dimethyl- 2-(2-methyl-6- quinoliny)- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	1.25 LC 337.0 [M+H] <sup>+</sup>	20
367		CH <sub>3</sub>	(3α,4β,7β,7a α)- Hexahydro-2- (5- isoquinoliny)- 4,7-dimethyl- 4,7-epoxy-1H- isoindole- 1,3(2H)-dione.	1.06 & 1.29 LC Rotational Isomers 323.0 [M+H] <sup>+</sup>	20

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
368		CH <sub>3</sub>	(3α,4β,7β,7a α)-2-(6-Benzothiazoly l)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isindole-1,3(2H)-dione.	2.15 LC 329.0 [M+H] <sup>+</sup>	20
369			[3α,4β,7β,7a α(E)]-4-[Octahydro-4-methyl-1,3-dioxo-7-(4-oxo-4-phenyl-2-butenyl)-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile.	3.50 LC 477.1 [M+H] <sup>+</sup>	265
370			(3α,4β,7β,7a α)-2-(4-Cyano-1-naphthalenyl)octahydro-N-(2-hydroxyphenyl)-7-methyl-1,3-dioxo-4,7-epoxy-4H-isindole-4-acetamide.	3.07 LC 482.14 [M+H] <sup>+</sup>	236

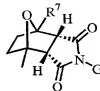
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
371			[3α,4β(E),7β,7α]-4-[Octahydro-4-methyl-7-[3-(6-methyl-2-pyridinyl)-2-propenyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	2.28 LC 464.19 [M+H] <sup>+</sup>	248
372			(3α,4β,7β,7α)-4-[Octahydro-4-methyl-7-[3-(6-methyl-2-pyridinyl)propyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	2.19 LC 466.32 [M+H] <sup>+</sup>	248, 249
373			[3αR-(3α,4β,7β,7α)-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-	3.73 LC 483.65 [M+H] <sup>+</sup>	<u>238i, 239i</u>

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			naphthalenecarbonitrile.		
374			[3aS-(3α,4β,7β,7aα)-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.73 LC	238ii, 239ii
375			[3aR-(3α,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.33 & 3.49 LC Rotational Isomers	238i, 239i
376			[3aS-(3α,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.73 LC 483.65 [M+H] <sup>+</sup>	238ii, 239ii
377			[3α,4β(E),7β,7aα]-4-[4-[3-(1H-Benzimidazol-2-yl)-2-propenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-	2.48 LC 489.26 [M+H] <sup>+</sup>	248

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			isoindol-2-yl]-1-naphthalene carbonitrile		
378			(3α,4β,7β,7aα)-4-[4-[3-(1H-Benzimidazol-2-yl)propyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalene carbonitrile	2.37 LC 491.26 [M+H] <sup>+</sup>	249

### Examples 379 to 381

- 5 Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 379 to 381 have the following structure (L is a bond):



- 10 where G, R<sup>7</sup>, the compound name, retention time, molecular mass, and the procedure employed, are set forth in **Table 6**. The chromatography techniques used to determine the compound retention times of **Table 6** are as follows: **LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing
- 15 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LCMS\*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LC** = YMC S5 ODS column 4.6 x 50 mm eluting




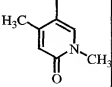


with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

The molecular mass of the compounds listed in **Table 6** were determined by MS (ES) by the formula  $m/z$ .

5

**Table 6**

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
379			(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )- 4-[4-(4- Fluorophenyl)m ethyl]octahydro- 7-methyl-1,3- dioxo-4,7-epoxy- 2H-isindol-2- yl]-2- (trifluoromethyl) benzonitrile.	3.75 LC	205
380		CH <sub>3</sub>	(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )- Hexahydro-4,7- dimethyl-2-(1- methyl-6-oxo-3- piperidiny)-4,7- epoxy-1H- isindole- 1,3(2H)-dione.	1.88 LC	27
381		CH <sub>3</sub>	(3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )- 2-(1,6-Dihydro- 1,4-dimethyl-6-	1.91 LC	27

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of <u>Ex.</u>
			oxo-3- pyridinyl)hexah ydro-4,7- dimethyl-4,7- epoxy-1H- isoindole- 1,3(2H)-dione.		

### Examples 382 to 383

- 5 Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 382 to 383 have the structure, compound name, retention time, molecular mass, and were prepared by the procedure employed, set forth in the following **Table 7**. The chromatography techniques used to determine the compound retention times of **Table**
- 10 **7** are as follows: **LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LCMS\*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes
- 15 containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in **Table 7** were determined by MS (ES) by the formula m/z.

Table 7

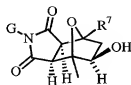
Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
382		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- 2-[4-Cyano-3- (trifluoromethyl) phenyl]octahydr o-1,3-dioxo-7-[2- (phenylmethoxy) ethyl]-4,7-epoxy- 4H-isindole-4- propanenitrile.	3.63 LC	255
383		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )- 2-[4-Cyano-3- (trifluoromethyl) phenyl]octahydr o-1,3-dioxo-7-[2- (phenylmethoxy) ethyl]-4,7-epoxy- 4H-isindole-4- propanenitrile	3.64 LC	255

5

**Examples 384 to 418**

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 384 to 418 have the following structure (L is a bond):

10


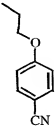



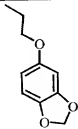

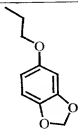
- where G, R<sup>7</sup>, the compound name, retention time, molecular mass, and the procedure employed, are set forth in **Table 8**. The absolute configuration for the following compounds was not determined. For simplicity in nomenclature, compound **243Di** is designated herein as having an "S" configuration and compound **243Dii** as having an "R" configuration. Enantiomerically pure products derived from compound **243Di** are designated herein as having an "S" configuration and enantiomerically pure products derived from compound **243Dii** are designated herein as having an "R" configuration.


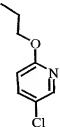

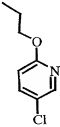

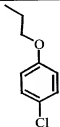
- 10 The chromatography techniques used to determine the compound retention times of **Table 8** are as follows: **LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LCMS\*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in **Table 8** were determined by MS (ES) by the formula m/z.


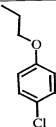

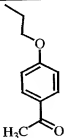
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
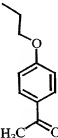

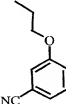

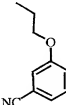
**Table 8**

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
384			(3α,4β,7β,7α)-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-	3.18 LC 494.40 [M+H] <sup>+</sup>	227, 228, 229





Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			yl]-1-naphthalenecar bonitrile.		
385			[3aS- (3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ ) ]-4-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octa hydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecar bonitrile.	3.19 LC 571.3 [M- H+OAc] <sup>-</sup>	243Di, 244i
386			[3aR- (3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ ) ]-4-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octa hydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecar bonitrile.	3.22 LC 571.2 [M- H+OAc] <sup>-</sup>	234Dii, 244ii





Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
387			[3aS- (3α,4β,7β,7αα) ]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.37 LC 562.2 [M-H+OAc] <sup>-</sup>	243Di, 244i
388			[3aR- (3α,4β,7β,7αα) ]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.37 LC 504.0 [M+H] <sup>+</sup>	243Dii, 244ii
389			[3aS- (3α,4β,7β,7αα) ]-4-[7-[2-(4-Chlorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-	3.51 LC 503.08 [M+H] <sup>+</sup>	243Di, 244i

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.		
390			[3aR-(3α,4β,7β,7α)-1-4-[7-[2-(4-Chlorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.51 LC 503.08 [M+H] <sup>+</sup>	243Dii, 244ii
391			[3aS-(3α,4β,7β,7α)-1-4-[7-[2-(4-Acetylphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.05 LC 511.13 [M+H] <sup>+</sup>	243Di, 244i


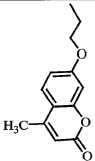

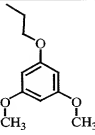
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
392			[3aR- (3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ ) ]-4-[7-[2-(4-Acetylphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.05 LC 503.13 [M+H] <sup>+</sup>	243Dii, 244ii
393			[3aS- (3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ ) ]-4-[7-[2-(3-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.09 LC 494.13 [M+H] <sup>+</sup>	243Di, 244i
394			[3aR- (3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ ) ]-4-[7-[2-(3-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-	3.09 LC 494.13 [M+H] <sup>+</sup>	243Dii, 244ii


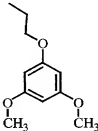

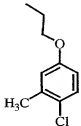

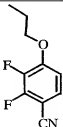



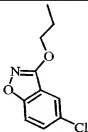

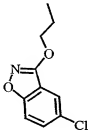
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			yl]-1-naphthalenecar bonitrile.		
395			[3aS- (3α,4β,7β,7α) ]-4-[Octahydro- 5-hydroxy-4- methyl-1,3- dioxo-7-[2- [(5,6,7,8- tetrahydro-1- naphthalenyl)o xy]ethyl]-4,7- epoxy-2H- isoindol-2-yl]-1- naphthalenecar bonitrile.	3.85 LC 523.17 [M+H] <sup>+</sup>	243Di, 244i
396			[3aR- (3α,4β,7β,7α) ]-4-[Octahydro- 5-hydroxy-4- methyl-1,3- dioxo-7-[2- [(5,6,7,8- tetrahydro-1- naphthalenyl)o xy]ethyl]-4,7- epoxy-2H- isoindol-2-yl]-1- naphthalenecar bonitrile.	3.85 LC 523.17 [M+H] <sup>+</sup>	243Dii, 244ii


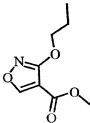

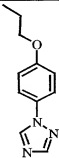

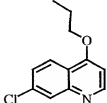
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
397			[3aS-(3α,4β,7β,7α)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.29 LC 537.13 [M+H] <sup>+</sup>	243Di, 244i
398			[3aR-(3α,4β,7β,7α)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.29 LC 537.13 [M+H] <sup>+</sup>	243Dii, 244ii


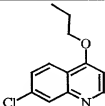

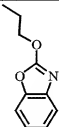
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
399			[3aS- (3α,4β,7β,7αα) ]-4-[7-[2-(4- Fluorophenoxy) ethyl]octahydro -5-hydroxy-4- methyl-1,3- dioxo-4,7-epoxy- 2H-isoindol-2- yl]-1- naphthalenecar bonitrile.	3.28 LC 487.11 [M+H] <sup>+</sup>	243Di, 244i
400			[3aR- (3α,4β,7β,7αα) ]-4-[7-[2-(4- Fluorophenoxy) ethyl]octahydro -5-hydroxy-4- methyl-1,3- dioxo-4,7-epoxy- 2H-isoindol-2- yl]-1- naphthalenecar bonitrile.	3.27 LC 487.11 [M+H] <sup>+</sup>	243Dii, 244ii
401			[3aS- (3α,4β,7β,7αα) ]-4-[Octahydro- 5-hydroxy-4- methyl-7-[2-[(4- methyl-2-oxo- 2H-1- benzopyran-7- yl)oxy]ethyl]-	3.15 LC 551.15 [M+H] <sup>+</sup>	243Di, 244i

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile.		
402			[3aR-(3α,4β,7β,7α)-1,4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile.	3.16 LC 551.10 [M+H] <sup>+</sup>	243Dii, 244ii
403			[3aS-(3α,4β,7β,7α)-1,4-[7-[2-(3,5-dimethoxyphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile.	3.28 LC 529.19 [M+H] <sup>+</sup>	243Di, 244i


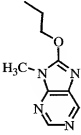

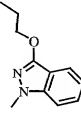
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
404			[3aR-(3α,4β,7β,7α)-1-4-[7-[2-(3,5-dimethoxyphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.26 LC 529.12 [M+H] <sup>+</sup>	243Dii, 244ii
405			[3aR-(3α,4β,7β,7α)-1-4-[7-[2-(4-chloro-3-methylphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.68 LC 517.33 [M+H] <sup>+</sup>	243Dii, 244ii
406			[3aR-(3α,4β,7β,7α)-1-4-[7-[2-(4-cyano-2,3-difluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-	3.23 LC 530.13 [M+H] <sup>+</sup>	243Dii, 244ii

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
			dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.		
407			[3aS-(3α,4β,7β,7α)-4-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.59 LC 602.1 [M-H+OAc] <sup>+</sup>	243Di, 252
408			[3aR-(3α,4β,7β,7α)-4-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.57 LC 602.0 [M-H+OAc] <sup>+</sup>	243Dii, 253


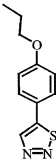

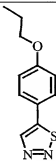

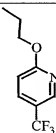
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
409			[3aR-(3α,4β,7β,7α)-1-3-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-6-hydroxy-7-methyl-1,3-dioxo-4,7-epoxy-4H-isindol-4-yl]ethoxy]-5-isoxazolecarboxylic acid, methyl ester.	2.90 LC 518.27 [M+H] <sup>+</sup>	243Dii, 253
410			[3aR-(3α,4β,7β,7α)-1-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[4-(1H-1,2,4-triazol-1-yl)phenoxy]ethyl]-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile.	2.93 LC 536.30 [M+H] <sup>+</sup>	243Dii, 244ii
411			[3aS-(3α,4β,7β,7α)-1-4-[7-[2-[(7-Chloro-4-quinolinyl)oxy]ethyl]octahydro-	2.52 LC 554.13 [M+H] <sup>+</sup>	243Di, 244i

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecar bonitrile, trifluoroacetate (1:1).		
412			[3aR-(3α,4β,7β,7aα)-4-[7-[2-[(7-Chloro-4-quinolinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecar bonitrile, trifluoroacetate (1:1).	2.53 LC 554.27 [M+H] <sup>+</sup>	243Dii, 244ii
413			[3aR-(3α,4β,5β,7β,7aα)-4-[7-[2-(2-Benzoxazolyloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-	3.13 LC 568.1 [M-H+OAc] <sup>-</sup>	243Dii, 244ii


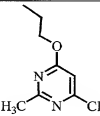


Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
			yl]-1-naphthalenecar bonitrile		
414			[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(9-methyl-9H-purin-8-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecar bonitrile	2.34 LC 525.2 [M+H] <sup>+</sup>	243Dii, 244ii
415			[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(1-methyl-1H-indazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecar bonitrile	3.33 LC	251,253

10024878.121901

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
416			[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[4-(1,2,3-thiadiazol-5-yl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.17 LC 553.10 [M+H] <sup>+</sup>	243Dii, 244ii
417			[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[4-(1,2,3-thiadiazol-5-yl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.20 LC 553.25 [M+H] <sup>+</sup>	243Dii, 244ii
418			[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[5-(trifluoromethyl)-2-pyridinyloxy]ethyl]-4,7-epoxy-2H-isoindol-2-	3.45 LC 538.23 [M+H] <sup>+</sup>	243Dii, 244ii

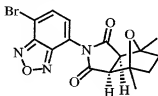
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Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
421			[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ $\alpha$ )]-4-[7-[2-[(6-Chloro-2-methyl-4-pyrimidinyl)oxy]ethyl]octahydro- o-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.02 LC	243Dii, 244ii

**Example 422**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Bromo-2,1,3-benzoxadiazol-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (422C)**

5

**A. 4-Bromo-7-nitrobenzofurazan (422A)**

- 10 To a solution of 2,6-dibromoaniline (1.0 g, 4.0 mmol) in  $\text{CHCl}_3$  (8 mL) was added a suspension of *m*CPBA (70% by HPLC, 1.4 g, 8.0 mmol)

in  $\text{CHCl}_3$  (8 mL) and the resulting mixture was stirred for 24 h at rt. The reaction mixture was diluted with  $\text{CHCl}_3$  and washed successively with 2%  $\text{Na}_2\text{S}_2\text{O}_3$  solution, 5%  $\text{Na}_2\text{CO}_3$  solution and brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to leave a solid, which was suspended, into DMSO (15 mL). To this suspension was added a solution of  $\text{NaN}_3$  (272 mg, 4.19 mmol) in DMSO (15 mL) at rt. The resulting mixture was stirred at rt until most of the nitrogen had evolved and was then quickly heated to  $120^\circ\text{C}$  for 3 min. The reaction mixture was cooled and poured onto crushed ice (100 g). After standing for 1 h the precipitates were filtered off, dried *in vacuo* and redissolved in conc.  $\text{H}_2\text{SO}_4$  (5 mL). To this solution was added a solution of  $\text{NaNO}_3$  (400 mg, 4.7 mmol) in 50%  $\text{H}_2\text{SO}_4$  (1.6 mL) and the temperature was maintained at  $60^\circ\text{C}$ . After the addition was complete, the mixture was heated at  $85^\circ\text{C}$  for 30 min, cooled to rt and poured onto crushed ice (40 g). EtOAc was added, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to leave a solid which was purified by flash chromatography (silica gel, EtOAc (20%) in hexanes) affording compound **422A** (785 mg, 81%) as a tan solid.

20

**B. 4-Bromo-7-aminobenzofurazan (422B)**



A solution of compound **422A** (563 mg, 2.31 mmol) in AcOH (5 mL) was heated to  $70^\circ\text{C}$  and  $\text{Fe}^0$  powder (258 mg, 4.62 mmol) was added in one portion. The resulting dark reaction mixture was stirred for 15 min, cooled to rt and concentrated under reduced pressure. The residue was taken up in EtOAc and the resulting solution was washed with sat.

Na<sub>2</sub>CO<sub>3</sub> solution. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 10-60% EtOAc in hexanes to give 470 mg (95%) of compound **422B** as a red solid.

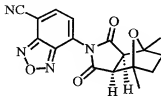
5

**C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Bromo-2,1,3-benzoxadiazol-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (**422C**)**

- 10 A mixture of compound **422B** (43 mg, 0.20 mmol), compound **20A** (45 mg, 0.23 mmol), MgSO<sub>4</sub> (60 mg, 0.50 mmol), Et<sub>3</sub>N (139  $\mu$ L, 1.0 mmol) and 1,2-dimethoxyethane (300  $\mu$ L) were placed in a sealed tube and heated at 135°C for 14 h. After cooling to rt the mixture was filtered through Celite eluting with MeOH to yield a dark solid which was purified
- 15 by flash chromatography on silica gel eluting with 5-40% EtOAc in hexanes to give 42 mg (54%) of compound **422C** as a yellow solid. HPLC: 99% at 2.96 min (retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2% H<sub>3</sub>PO<sub>4</sub>, 4 mL/min, monitoring at 220 nm). <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>, 400 MHz):
- 20  $\delta$  = 8.00 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 3.31 (s, 2H), 1.98-1.93 (m, 2H), 1.74-1.69 (m, 2H), 1.57 (s, 6H).

**Example 423**

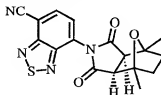
- 25 **(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzoxadiazole-4-carbonitrile (**423**)**



To a solution of compound **422C** (42 mg, 0.11 mmol) in DMA (1 mL) was added CuCN (20 mg, 0.22 mmol) and the resulting mixture was heated at 150°C for 5 h. The mixture was allowed to cool to rt and partitioned between EtOAc and aqueous NaCN solution (5 g/50 mL). The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 20-70% EtOAc in hexanes to give 13 mg (35%) of compound **423** as a yellow oil. HPLC: 99% at 2.66 min (retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2% H<sub>3</sub>PO<sub>4</sub>, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 396.9 [M-H+OAc].

#### Example 424

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-7-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (424B)**



#### A. 4-Cyano-7-amino-benzothiadiazole (424A)



A solution of 2-cyano-5-nitrophenylenediamine (78 mg, 0.44 mmol, prepared as described in WO 0076501) in SOCl<sub>2</sub> (2 mL) was heated to reflux for 3 h. The resulting mixture was allowed to cool to rt and was then poured into ice/water. CH<sub>2</sub>Cl<sub>2</sub> was added, the layers were separated and the aqueous layer was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over MgSO<sub>4</sub>, concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 50% EtOAc in hexanes

to give 4-cyano-7-nitrobenzothiadiazole. This material was dissolved in AcOH (2 mL) containing EtOAc (1 mL) and H<sub>2</sub>O (0.2 mL) and heated to 70°C. At this temperature Fe<sup>0</sup> powder (78 mg, 1.41 mmol) was added in one solid portion and the dark mixture was stirred for 20 min and then cooled to rt. The reaction mixture was filtered through Celite eluting with EtOAc, washed with sat. Na<sub>2</sub>CO<sub>3</sub> solution, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 20-70% EtOAc in hexanes to yield 47 mg (67%) of compound **424A** as a brown solid.

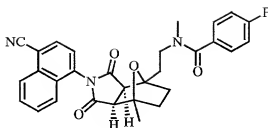
**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-7-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (424B)**

A mixture of compound **424A** (35 mg, 0.20 mmol), compound **20A** (45 mg, 0.23 mmol), MgSO<sub>4</sub> (60 mg, 0.50 mmol), Et<sub>3</sub>N (139  $\mu$ L, 1.0 mmol) and DME (200  $\mu$ L) was placed in a sealed tube and heated at 135°C for 14 h. After cooling to rt the mixture was filtered through Celite eluting with MeOH to yield a dark solid which was purified by a combination of flash chromatography on silica gel eluting with 10-50% EtOAc in hexanes reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 27-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min) to give 36 mg (51%) of compound **424B** as a yellow solid. HPLC: 98% at 2.45 min (retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2% H<sub>3</sub>PO<sub>4</sub>, 4 mL/min, monitoring at 220 nm). MS (DCI): m/z 355.0 [M+H]<sup>+</sup>.

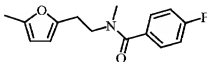
**Example 425**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-N-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isindol-4-yl]ethyl]-4-fluoro-N-methylbenzamide (425B)**





**A. 4-Fluoro-*N*-methyl-*N*-[2-(5-methyl-furan-2-yl)-ethyl]-benzamide (425A)**



5

NaH (60% dispersion in oil, 65 mg, 1.63 mmol) was added portionwise to a solution of 4-fluoro-*N*-[2-(5-methyl-2-furanyl)ethyl]benzamide (269 mg, 1.09 mmol, **237A**) in THF (5 mL). After gas evolution ceased, iodomethane (0.14 mL, 2.18 mmol) was added drop-wise. Once HPLC analysis showed the reaction to be 50% complete, the mixture was concentrated under reduced pressure and resubjected to the above conditions. After all the starting material was consumed, H<sub>2</sub>O was added and the resulting mixture was extracted with EtOAc (2 X 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 20% acetone/CHCl<sub>3</sub> gave 238 mg (84%) of compound **425A**. HPLC: 98% at 2.94 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* [M+H] = 262.38.

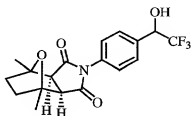
**20 B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-*N*-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]-4-fluoro-*N*-methylbenzamide (425B)**

A solution of compound **425A** (183 mg, 0.75 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (174 mg, 0.75 mmol) in benzene (1 mL) was heated at 60°C for 15 hr. The reaction mixture was concentrated under reduced pressure to give 357 mg crude intermediate. The crude intermediate (156 mg) was

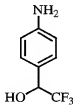
dissolved in EtOAc (6 mL) and 10% Pd/C (16 mg) was added and the mixture was stirred under a hydrogen balloon overnight. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) gave 160.3 mg (72%) of compound **425B** as an off-white solid. HPLC: 99% at 3.23 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z [M+H] = 512.19.

#### Example 426

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-[4-(2,2,2-trifluoro-1-hydroxyethyl)phenyl]-4,7-epoxy-1H-isoidole-1,3(2H)-dione (426B)**



#### A. **1-(4-Amino-phenyl)-2,2,2-trifluoro-ethanol (426A)**



Compound **426A** was made according to the procedure described in Stewart, R. et al. *Can. J. Chem.* 58, 2491-2496 (1980). NaBH<sub>4</sub> (47 mg, 1.235 mmol) was added to a solution of p-aminotrifluoroacetophenone (155.7 mg, 0.823 mmol, synthesized as described by Klabunde, K. J. et al. *J. Org. Chem.* 35, 1711-1712 (1970)) in isopropanol (3 mL) at rt. After 30 min the reaction was quenched with phosphate buffer (pH 7.2), diluted with H<sub>2</sub>O and extracted with EtOAc (2 X 10 mL).

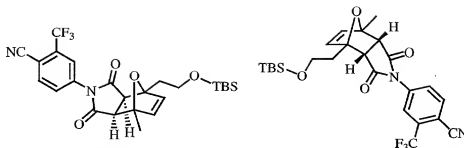
The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give 154 mg (98%) of compound **426A** as a tan solid. The material was used directly in the next step without purification. HPLC: 99% at 0.42 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$   $[\text{M}+\text{H}] = 192.13$ .

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-[4-(2,2,2-trifluoro-1-hydroxyethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (426B)**

A mixture of compound **426A** (75.3 mg, 0.394), compound **20A** (51.5 mg, 0.262 mmol), triethylamine (0.15 mL) and  $\text{MgSO}_4$  (50 mg) in toluene (1 mL) was heated in a sealed tube to 135°C for 15 hr. The mixture was filtered and concentrated under reduced pressure. Purification by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) gave 63.1 mg (65%) of compound **426B** as a white solid. HPLC: 98% at 2.49 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$   $[\text{M}+\text{H}] = 370.16$ .

**Example 427**

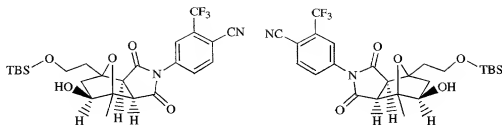
**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & (3 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ )-4-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (427i & 427ii)**



- Compound **204A** (2.00 g, 8.50 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (1.50 g, 5.60 mmol) were mixed in benzene (5.0 mL) and heated at 60°C for 14 h, then cooled to 25°C. The solvent was removed at 40°C under vacuum for 1 h to give the crude material which was purified by flash chromatography on SiO<sub>2</sub> eluting with 0.5% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> to give 2.0 g of compound **427i** and 1.3 g of compound **427ii**, both as light brown solids. Compound **427i**: HPLC: 95% at 4.200 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 507.1 [M+H]<sup>+</sup>. Compound **427ii**: HPLC: 95% at 4.20 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 507.1 [M+H]<sup>+</sup>.

#### Example 428

- [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (428i & 428ii)



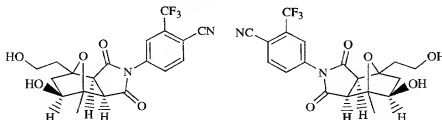
- Compound **427i** (1.40 g, 2.77 mmol) and  $\text{RhCl}(\text{PPh}_3)_3$  (0.128 g, 0.14 mmol) were mixed in a flask. The flask was then evacuated and filled with argon three times, followed by the syringe addition of THF (3.0 mL). Once all particulates were dissolved, catecholborane (0.59 mL, 5.54 mmol) was added dropwise. The reaction mixture was stirred at 25°C under argon for 30 min, then cooled to 0 °C. Phosphate buffer (pH 7, 20 mL) was added, followed by EtOH (10 mL), 30%  $\text{H}_2\text{O}_2/\text{H}_2\text{O}$  (2 mL). The reaction mixture was stirred at 0°C for 3 h, then extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with 1 N NaOH (25 mL), 10%  $\text{Na}_2\text{SO}_3$  (25 mL) and brine (25 mL). The crude material was then concentrated *in vacuo* and purified by flash chromatography on  $\text{SiO}_2$  eluting with 2% EtOAc/ $\text{CH}_2\text{Cl}_2$  to 10% EtOAc/ $\text{CH}_2\text{Cl}_2$  to give 0.63 g of a racemic mixture of compounds **428i** & **428ii** as a light yellow solid. HPLC: 99% at 3.867 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  525.1 [M+H]
- The racemic mixture of compounds **428i** & **428ii** was separated by normal phase preparative chiral HPLC using a Chiracel OD column (5 cm x 50 cm), eluting with 13% solvent B (EtOH) in solvent A (hexanes), flow rate: 50 mL/min. Compound **428i** eluted from 34 min to 38 min and compound **428ii** eluted from 44 min to 49 min. Enantiomeric excess was determined by chiral HPLC. Compound **428i**: >99% ee (12.576 min (retention time) (Chiralcel OJ column 4.6 x 250 mm eluting with isocratic 85% heptane / 15% MeOH/ethanol (1:1), 1 mL/min, monitoring at 220 nm,

40°C). Compound **428ii**: 99% ee (18.133 min (retention time) (Chiralcel OJ column 4.6 x 250 mm eluting with isocratic 85% heptane / 15% MeOH/ethanol (1:1), 1 mL/min, monitoring at 220 nm, 40°C).

The absolute configurations for compounds **428i** & **428ii** were not established. For simplicity in nomenclature, compound **428i** is designated herein as having an "R" configuration and compound **428ii** as having an "S" configuration. Enantiomerically pure products derived from compound **428i** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **428ii** are designated herein as having an "S" configuration.

#### Example 429

**[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (**429i** & **429ii**)**



20

Compound **428i** (180 mg, 0.34 mmol) was dissolved in 2% HCl/EtOH (5.0 mL). After 30 min, saturated NaHCO<sub>3</sub> was added and the aqueous layer was extracted with dichloromethane (20 mL x 3), washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub> to give 135 mg of compound **429i** as a white solid. HPLC: 99% at 2.257 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4

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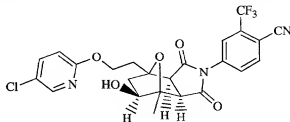
minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  411.1  $[M+H]^+$ .

The above procedure was repeated with compound **428ii** to yield the desired diol compound **429ii** in similar yield.

5

#### Example 430

**[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (430)**



10

Triphenylphosphine (0.026 g, 0.098 mmol) and DBAD (0.023 g, 0.098 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, 2-hydroxy-6-chloropyridine (0.016 g, 0.100 mmol) was added, the mixture was allowed to stir for 10 min and compound **429i** (0.020 g, 0.049 mmol) was added. The reaction mixture was stirred at 25°C for 2 h and then the crude material was purified by preparative TLC, eluting with 10% acetone/ $CHCl_3$ , to give 0.014 g of compound **430** as a light brown solid. HPLC: 100% at 3.370 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  522.08  $[M+H]^+$ .

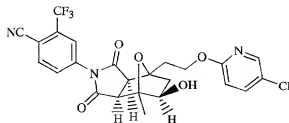
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#### Example 431

**[3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (431)**

25

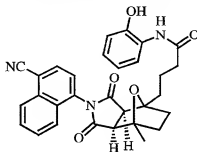


Triphenylphosphine (0.026 g, 0.098 mmol) and DBAD (0.023 g, 0.098 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, 2-hydroxy-6-chloropyridine (0.016 g, 0.100 mmol) was added, the mixture was allowed to stir for 10 min and compound **429ii** (0.020 g, 0.049 mmol) was added. The reaction mixture was stirred at 25°C for 2 h and then the crude material was purified by preparative TLC, eluting with 10% acetone/CHCl<sub>3</sub>, to give 0.015 g of compound **431** as a light brown solid. HPLC: 100% at 3.370 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 522.08 [M+H]<sup>+</sup>.

15

**Example 432**

**(3α,4β,7β,7α)-2-(4-Cyano-1-naphthalenyl)octahydro-N-(2-hydroxyphenyl)-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-butanamide (432)**



20

Compound **262** (0.100 g, 0.239 mmol) was dissolved in DMF (anhydrous, 1.5 mL), BOP (0.211 g, 0.478 mmol) was added followed by 2-aminophenol (0.052 g, 0.478 mmol) and *N*-methyl morpholine (0.052 mL,

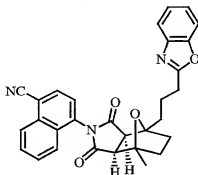


0.478 mmol). The reaction mixture was stirred at 25°C under argon for 3 h, then the crude material was purified by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to give  
 5 0.060 g of compound **432** as a light brown solid. HPLC: 100% at 3.037 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 510.34 [M+H]<sup>+</sup>.

10

**Example 433**

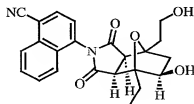
**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[3-(2-Benzoxazolyl)propyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile**

**(433)**

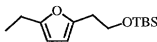
15 Triphenylphosphine (0.031 g, 0.118 mmol) and DBAD (0.027 g, 0.118 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, compound **432** (0.030 g, 0.059 mmol) was added. The reaction mixture was stirred at 25°C for 2 h and then the crude material was purified by reverse phase preparative HPLC (YMC S5  
 20 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to give 0.018 g of compound **433** as a light brown solid. HPLC: 100% at 3.357 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min,  
 25 monitoring at 220 nm). MS (ES): m/z 492.37 [M+H]<sup>+</sup>.

Example 434

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-Ethyl-2,3,4,5-tetrahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (434C)

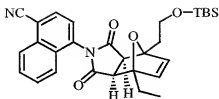


A. **tert-Butyl-[2-(5-ethyl-furan-2-yl)-ethoxy]-dimethyl-silane (434A)**



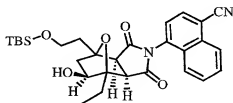
Imidazole (255 mg, 3.75 mmol) and TBSCl (414 mg, 2.75 mmol) were added to the solution of **245A** (350 mg, 2.5 mmol) in DMF (4 mL). The mixture was stirred at rt for 15 hr and then 100 mg (0.66 mmol) of additional TBSCl was added to drive the reaction to completion. After stirring for an additional hour, the reaction mixture was diluted with diethylether (100 mL) and washed with water (20 mL), 1 N HCl (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give 509 mg of compound **434A** (80.3%) as a yellow oil.

B. **(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[[1,1-Dimethylethyl)-dimethylsilyl]oxy]ethyl]-4-ethyl-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (434B)**



A solution of compound **434A** (509 mg, 2.00 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (498 mg, 2.00 mmol) in benzene (2 mL) was heated at 60°C for 18 h. The reaction mixture was concentrated under reduced pressure to give 992 mg (99%) of crude compound **434B**, which was used directly in the next step without further purification.

- 10 C. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-[(1,1-Dimethylethyl)-dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**434C**)



15

A mixture of compound **434B** (992 mg, 1.98 mmol) and  $\text{RhCl}_2(\text{PPh}_3)_3$  (183 mg, 0.198 mmol) was evacuated and filled with argon (3X). THF (20 mL) was added and once all particulates had dissolved, catecholborane (0.42 mL, 3.96 mmol) was slowly added dropwise. When the formation of product ceased, as was determined by HPLC, the reaction mixture was cooled to 0°C and quenched with phosphate buffer (34 mL, pH 7.2) followed by the addition of EtOH (19 mL) and 30%  $\text{H}_2\text{O}_2$  (2.9 mL). After 2 h, additional phosphate buffer (6.8 mL, pH 7.2), EtOH (3.8 mL) and  $\text{H}_2\text{O}_2$  (0.6 mL) were added. The reaction mixture was stirred at rt for 3 h. Once

the boronate intermediate was consumed, the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (300 mL) and the combined organic layers were washed with 1 N NaOH, 10% aq.  $\text{NaHSO}_3$  and brine and then dried over  $\text{Na}_2\text{SO}_4$ .

Purification by flash chromatography on silica gel eluting with 10%

- 5 MeOH/ $\text{CH}_2\text{Cl}_2$  gave 75 mg (9.3%) of compound **434C** as a gray solid. HPLC conditions: 97% at 2.43 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2%  $\text{H}_3\text{PO}_4$ , detecting at 220 nm). MS (ES):  $m/z$  407.18  $[\text{M}+\text{H}]^+$ .

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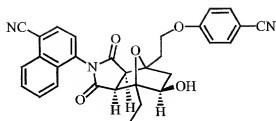
**D. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-Ethyl octahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (434D)**

- 15 Compound **434C** (24 mg, 0.046 mmol) was dissolved in 2% conc. HCl/EtOH (0.8 mL) and the mixture was stirred at rt for 20 min. Cold sat.  $\text{NaHCO}_3$  was added to the mixture until the solution was basic (pH 8). The reaction was extracted with EtOAc (3 x 2 mL) and the combined organic layers were washed with brine (2 x 5 mL) and dried over
- 20 anhydrous sodium sulfate. Concentration *in vacuo* gave 14 mg (75%) of compound **434D** as a white solid. HPLC: 95% at 2.40 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2%  $\text{H}_3\text{PO}_4$ , monitoring at 220 nm).

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#### Example 435

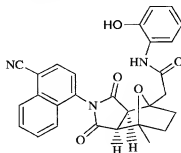
**(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyl octahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (435)**



- DBAD (39.6 mg, 0.172 mmol) was added to a solution of  $\text{PPh}_3$  (45.1 mg, 0.172 mmol) in THF (0.8 mL). After stirring for 10 min, 4-cyanophenol (20.5 mg, 0.172 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound **434C** (25.0 mg, 0.062 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by Prep TLC eluting with 10% acetone/ $\text{CHCl}_3$  gave 18.1 mg (0.036 mmol, 57.6%) of compound **435**. HPLC conditions: 96% at 3.15 min (retention time) (YMC S5 ODS 4.6 X 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2%  $\text{H}_3\text{PO}_4$ , detecting at 220 nm). MS (ES):  $m/z$  508.14  $[\text{M}+\text{H}]^+$ .

#### Example 436

- (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(4-Cyano-1-naphthyl)octahydro-*N*-(2-hydroxyphenyl)-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-ethanamide (436)**

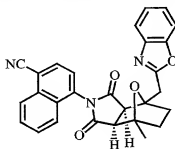


- Compound **234B** (0.100 g, 0.256 mmol) was dissolved in DMF (anhydrous, 1.5 mL), BOP (0.225 g, 0.51 mmol) was added followed by 2-aminophenol (0.056 g, 0.51 mmol) and *N*-methyl morpholine (0.056 mL, 0.51 mmol). The reaction mixture was stirred at 25°C under argon for 3 h,

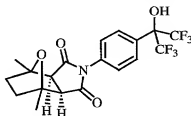
then the crude material was purified by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to give 0.078 g of compound **436** as a light brown solid. HPLC: 100% at 3.037 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 482.34 [M+H]<sup>+</sup>.

#### Example 437

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-(2-Benzoxazolylmethyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (437)**



Triphenylphosphine (0.082 g, 0.312 mmol) and DBAD (0.072 g, 0.312 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, compound **436** (0.075 g, 0.156 mmol) was added. The reaction mixture was stirred at 25°C for 2 h and then the crude material was purified by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to give 0.052 g of compound **437** as a light brown solid. HPLC: 100% at 3.443 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 464.18 [M+H]<sup>+</sup>.

**Example 438****(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-4,7-epoxy-1H-isoindole-****1,3(2H)-dione (438)**

5

A mixture of 2-(4'-aminophenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (95.7 mg, 0.369), compound **20A** (48.3 mg, 0.246 mmol), triethylamine (0.15 mL) and MgSO<sub>4</sub> (50 mg) in toluene (1 mL) was heated in a sealed tube to 135°C overnight. The mixture was filtered and concentrated under reduced pressure. Purification by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) gave 44.0 mg (41%) of compound **438** as a white solid. HPLC: 99% at 3.10 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z [M+H] = 438.14.

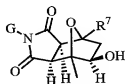
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**Examples 439 to 454**

20

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 439 to 454 have the following structure (L is a bond):



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
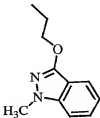

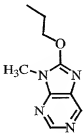
where G, R<sup>7</sup>, the compound name, retention time, molecular mass, and the procedure employed, are set forth in **Table 9**. The absolute configuration


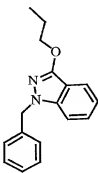

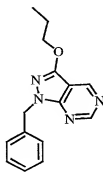
- for the following compounds was not determined. For simplicity in nomenclature, compound **243Di** is designated herein as having an "S" configuration and compound **243Dii** as having an "R" configuration. Enantiomerically pure products derived from compound **243Di** are designated herein as having an "S" configuration and enantiomerically pure products derived from compound **243Dii** are designated herein as having an "R" configuration. Similarly, compound **428i** is designated herein as having an "S" configuration and compound **428ii** as having an "R" configuration. Enantiomerically pure products derived from compound **428i** are designated herein as having an "S" configuration and enantiomerically pure products derived from compound **428ii** are designated herein as having an "R" configuration.

- The chromatography techniques used to determine the compound retention times of **Table 9** are as follows: **LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LCMS\*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.
- The molecular mass of the compounds listed in **Table 9** were determined by MS (ES) by the formula m/z.


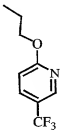


Table 9


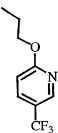

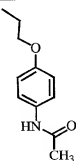
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
439			[3a <i>R</i> - (3α,4β,5β,7β, 7α)]-4- [Octahydro-5- hydroxy-4- methyl-7-[2- [(1-methyl- 1H-indazol-3- yl)oxy]ethyl]- 1,3-dioxo-4,7- epoxy-2H- isoindol-2-yl]- 1- naphthalenec arbonitrile	3.33 LC 523.3 [M+H] <sup>+</sup>	251, 253
440			[3a <i>R</i> - (3α,4β,5β,7β, 7α)]-4- [Octahydro-5- hydroxy-4- methyl-7-[2- [(9-methyl- 9H-purin-8- yl)oxy]ethyl]- 1,3-dioxo-4,7- epoxy-2H-	2.34 LC 525.2 [M+H] <sup>+</sup>	251, 253


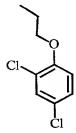

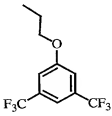
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time <u>Min./</u> <u>Molecular</u> <u>Mass</u>	Procedure of Ex.
			isoindol-2-yl]- 1- naphthalenec arbonitrile		
441			[3aR- (3α,4β,5β,7β, 7α)]-4- [Octahydro-5- hydroxy-4- methyl-1,3- dioxo-7-[2-[[1- (phenylmethyl )-1H-indazol- 3- yl]oxy]ethyl]- 4,7-epoxy-2H- isoindol-2-yl]- 1- naphthalenec arbonitrile	3.73 LC	251, 253
442			[3aR- (3α,4β,5β,7β, 7α)]-4- [Octahydro-5- hydroxy-4- methyl-1,3- dioxo-7-[2-[[1-	3.37 LC	251, 253


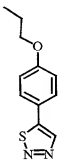

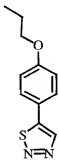
1002487.121901


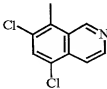
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			(phenylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
443			[3aS-(3α,4β,5β,7β,7α)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.45 LC 538.23 [M+H] <sup>+</sup>	243Di, 244i


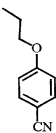

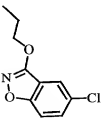
10024878-121901

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
444			[3aR-(3α,4β,5β,7β,7α)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile	3.46 LC 538.24 [M+H] <sup>+</sup>	243Dii, 244ii
445			[3aR-(3α,4β,5β,7β,7α)]-N-[4-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-7H-isindol-7-	2.747 LC 526.28 [M+H] <sup>+</sup>	243Dii, 244ii


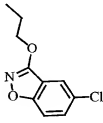

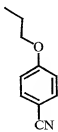
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			yl]ethoxy]phenyl]acetamide		
446			[3a <i>R</i> -(3α,4β,5β,7β,7α)]-4-[7-[2-(2,4-Dichlorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2 <i>H</i> -isoindol-2-yl]-1-naphthalenecarbonitrile	3.71 LC 537.17 [M+H] <sup>+</sup>	243Dii, 244ii
447			[3a <i>R</i> -(3α,4β,5β,7β,7α)]-4-[7-[2-[3,5-Bis(trifluoromethyl)phenoxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-	3.89 LC 605.25 [M+H] <sup>+</sup>	243Dii, 244ii

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			epoxy-2H- isoindol-2-yl]- 1- naphthalenec arbonitrile		
448			[3aS- (3α,4β,5β,7β, 7α)]-4- [Octahydro-5- hydroxy-4- methyl-1,3- dioxo-7-[2-[4- (1,2,3- thiadiazol-5- yl)phenoxy]et hyl]-4,7- epoxy-2H- isoindol-2-yl]- 1- naphthalenec arbonitrile	3.14 LC 553.1 [M+H] <sup>+</sup>	243Di, 244i
449			[3aR- (3α,4β,5β,7β, 7α)]-4- [Octahydro-5- hydroxy-4- methyl-1,3-	3.15 LC 553.23 [M+H] <sup>+</sup>	243Dii, 244ii

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			dioxo-7-[2-[4-(1,2,3-thiadiazol-5-yl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
450			[3aR-(3α,4β,5β,7β,7α)]-4-[7-[2-[(5,7-Dichloro-8-quinolinyloxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.70 LC 588.26 [M+H] <sup>+</sup>	243Dii, 244ii

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
451			[3aS-(3α,4β,5β,7β,7α)]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile	3.087 LC 512.13 [M+H] <sup>+</sup>	431
452			[3aS-(3α,4β,5β,7β,7α)]-4-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-	3.563 LC 562.08 [M+H] <sup>+</sup>	431

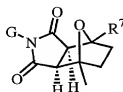


Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			isoindol-2-yl]- 2- (trifluorometh yl)benzonitrile		
453			[3aR- (3α,4β,5β,7β, 7α)]-4-[7-[2- [(5-Chloro-1,2- benzisoxazol- 3- yl)oxy]ethyl]oc tahydro-5- hydroxy-4- methyl-1,3- dioxo-4,7- epoxy-2H- isoindol-2-yl]- 2- (trifluorometh yl)benzonitrile	3.57 LC 562.08 [M+H] <sup>+</sup>	430
454			[3aR- (3α,4β,5β,7β, 7α)]-4-[7-[2- (4- Cyanophenox y)ethyl]octahy dro-5-	3.087 LC 512.08 [M+H] <sup>+</sup>	430

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-(trifluoromethyl)benzonitrile		

### Examples 455 to 457

- 5 Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 455 to 457 have the following structure (L is a bond):


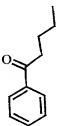



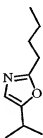

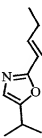
- 10 where G, R<sup>7</sup>, the compound name, retention time, molecular mass, and the procedure employed, are set forth in **Table 10**. The absolute configuration for the following compounds was not determined. For simplicity in nomenclature, compound **238i** is designated herein as having
- 15 an "R" configuration and compound **238ii** as having an "S" configuration. Enantiomerically pure products derived from compound **238i** are designated herein as having an "R" configuration and enantiomerically pure products derived from compound **238ii** are designated herein as having an "S" configuration.

The chromatography techniques used to determine the compound retention times of **Table 10** are as follows: **LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LCMS\*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. **LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H<sub>2</sub>O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in **Table 10** were determined by MS (ES) by the formula m/z.

10

**Table 10**

Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./Molecular Mass	Procedure of Ex.
455			(3α,4β,5β,7β,7α)-4-[Octahydro-4-methyl-1,3-dioxo-7-(4-oxo-4-phenylbutyl)-4,7-epoxy-2H-isindol-2-yl]-1-naphthalene carbonitrile	3.53 LC 479.35 [M+H] <sup>+</sup>	265, 266

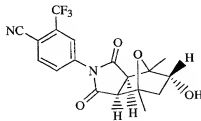
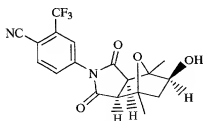
Ex. No	G	R <sup>7</sup>	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
456			(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4-methyl-7-[3-[5-(1-methylethyl)-2-oxazolyl]propyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.547 LC 484.28 [M+H] <sup>+</sup>	248, 249
457			[3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ (E)]-4-[Octahydro-4-methyl-7-[3-[5-(1-methylethyl)-2-oxazolyl]-2-propenyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.66 LC 482.28 [M+H] <sup>+</sup>	248, 249

<u>Ex.</u> <u>No</u>	<u>G</u>	<u>R'</u>	<u>Compound</u> <u>Name</u>	<u>Retention</u> <u>Time</u> <u>Min./</u> <u>Molecular</u> <u>Mass</u>	<u>Procedure</u> <u>of</u> <u>Ex.</u>
			arbonitrile		

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**Example 458**

- 5 **(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (3 $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221B & 222D)**



- Compound **20B** was converted to compounds **221B** and **222D** (also synthesized as compounds **221B** and **222D**) by biotransformation.
- Compound **20B** was hydroxylated by *Amycolatopsis orientalis* (ATCC 43491). A 1 mL culture from a frozen vial was used to inoculate 100 mL medium in a 500 mL portion Erlenmeyer flask and the flask was incubated at 28°C, at 200 rpm for 3 days. A 10 mL portion of this culture was used to inoculate 100 mL medium in a 500 mL Erlenmeyer flask and the flask was incubated at 28°C, at 200 rpm for 1 day. 10 mL portions of the 1-day culture were distributed to each of three 50 mL flasks. Compound **20B** (3 mg in 0.1 mL methanol) was added to each culture and the incubations were continued for 3 days. The culture broth in each flask was extracted with 20 mL ethyl acetate, and the pooled ethyl acetate extracts were evaporated to dryness at 40°C under a nitrogen stream. The residue was dissolved in 1.2 mL methanol and analyzed by HPLC, LC/MS and LC/NMR. The solution contained 2.5 mg of remaining Compound **20B**, 1.6 mg of compound **221B**, and 1.3 mg of compound **222D**. MS and NMR analyses were in agreement with the structures shown above.
- 25 Medium:** 0.5% toasted nutrisoy, 2% glucose, 0.5% yeast extract, 0.5% K<sub>2</sub>HPO<sub>4</sub>, 0.5% NaCl, adjusted to pH 7 with HCl (R. V. Smith and J. P. Rosazza, Arch. Biochem. Biophys., **161**, 551-558 (1974))
- HPLC Analysis

- Column: Phenomenex Luna C18, 150x2 mm, 5 $\mu$   
 mobile phase: solvent A: 95% 20 mM ammonium acetate pH 5.1, 5% acetonitrile  
 solvent B: 95% acetonitrile, 5% 20 mM ammonium acetate pH 5.1  
 linear gradient going from 100% solvent A to 5% solvent A in 25 minutes followed  
 5 by equilibration at 100% solvent A for 8 minutes.  
 temperature: 40 °C  
 detection: 250 nm  
 injection volume: 1  $\mu$ L  
 retention times: compound **20B**, 20.8 min; compound **221B**, 16.5 min; compound  
 10 **222D**, 17.8 min

#### HPLC Conditions

- Chiral HPLC conditions were employed for the separation of enantiomers and  
 achiral HPLC conditions were employed for the separation of diastereomers of the  
 hydroxylated analogs of compound **20B** (i.e., compounds **221B** and **222D** and  
 15 compounds **254i** and **254ii**)

Two methods were used under chiral HPLC conditions, reverse phase (RP) for  
 chiral analysis of biotransformation products in biological samples and normal phase  
 (NP) for non-biological samples.

#### **Chiral RP-HPLC Condition**

Column:	CHIRALPAK AD-R 4.6 x 250 mm, 10 $\mu$
Temperature:	40°C
Injection Volume:	5 or 20 $\mu$ L
Mobile Phase:	A: MeCN B: H <sub>2</sub> O Isocratic, 30% of A, 18 min.
Flow Rate:	1 mL/min.
UV Detection:	242 nm

**Chiral NP-HPLC Condition**

Column: CHIRALPAK AD  
 4.6 x 250 mm, 10  $\mu$   
 Temperature: 25°C  
 Injection Volume: 5 or 20  $\mu$ L  
 Mobile Phase: A: Heptane  
 B: MeOH/Ethanol  
 (1:1)  
 Isocratic, 80% of A, 20 min.  
 Flow Rate: 1 mL/min.  
 UV Detection: 242 nm

Under these conditions compounds **254i** and **254ii** had retention times of 8.5 minutes and 9.85 minutes, respectively.

Reverse phase HPLC was employed for the separation of the diastereomeric compounds **221B** and **222D**:

**Mobile Phase:**

Solvent A: 95% 20 mM ammonium acetate pH 5.1, 5% acetonitrile  
 Solvent B: 95% acetonitrile, 5% 20 mM ammonium acetate pH 5.1

**Gradient:**

Linear gradient going from 100% solvent A to 5% solvent A in 25 minutes followed by equilibration at 100% solvent A for 8 minutes. Total run time of 36 minutes.

**Flow Rate:**

0.2 mL/min

**Column:**

Phenomenex Luna 5 micron C<sub>18</sub> 150X2.0 mm id

**Detection:**

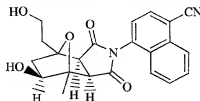
UV detection at 242 nm



Under these conditions, compounds **221B** and **222D** had retention times of 18.983 min and 20.362 min, respectively.

### Example 459

- 5     **(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (459)**



- 10     Compounds **223A** and **331** were converted to compound **459** by biotransformation.

### Microbial hydroxylation of compound **223A**

#### 1. Reaction

- 15     To a 500 mL flask containing 100 mL of the transformation medium was added one frozen vial (approximately 2 mL) of *Streptomyces griseus* ATCC 10137. The transformation medium was prepared as follows: to a 2 L plastic beaker was added 20 g of dextrose, 5.0 g of yeast extract, 5.0 g of soybean meal, 5.0 g of sodium chloride, 5.0 g of potassium phosphate
- 20     (diabasic) and 1 L of deionized water, and the mixture was stirred at room temperature for 3 to 30 min. The pH of the mixture was then adjusted to 7.0 with 1 N HCl or 1 N NaOH. The resulting mixture was dispensed into 500 mL flasks (100 mL per flask). The flasks were covered with Bio/Wrap and autoclaved at 121°C for 15 min. and cooled down to room
- 25     temperature before use.

- The culture was incubated at 28°C and at 250 rpm for 24 hours. Ten mL of the resulting culture was transferred to a 50 mL flask, to which 1 mg of compound **223A** in 0.2 mL ethanol was added. The flask was incubated at 28°C and 250 rpm for 24
- 30     hours, and the reaction culture was extracted with EtOAc (10 mL). The EtOAc

extract was dried under N<sub>2</sub> and the residue was dissolved in 1 mL of MeOH (reaction extract).

## **2. Product analysis**

### **5 HPLC:**

10  $\mu$ L of the reaction extract was injected into HPLC column (YMC ODS-AQ C-18 column, 150 x 6.0 mm i.d.). The column was eluted with 1 mM HCl in water/CH<sub>3</sub>CN at 1.2 mL/min flow rate: 30 to 60% CH<sub>3</sub>CN over 8 min, 60 to 85% CH<sub>3</sub>CN over 0.5 min, 85% CH<sub>3</sub>CN for 1 min, 85 to 30% CH<sub>3</sub>CN over 0.5 min. The eluents were monitored at 300 nm. Two major peaks with about a 1 to 1 area ratio were observed, which had the same UV spectra as those of compounds **459** and **331**, and had retention times of 4.55 min and 7.23 min, respectively, matching the retention times of authentic samples of compound **459** (4.53 min) and compound **331** (7.2 min).

### **LC/MS**

The reaction extract: two major UV peaks.

Peak 1, Tr 4.68 min: 391 [M+H]<sup>+</sup>, 343, 319, 303, 289

20 Peak 2, Tr 5.35 min: 375 [M+H]<sup>+</sup>, 345

### **Authentic samples**

Compound **459**, Tr 4.82 min: 391 [M+H]<sup>+</sup>, 343, 319, 289

Compound **331**, Tr 5.48 min: 375 [M+H]<sup>+</sup>, 345

### **Microbial hydroxylation of Compound 331**

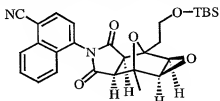
To a 500 mL flask containing 100 mL of the transformation medium was added one frozen vial (approximately 2 mL) of *Streptomyces griseus* ATCC 10137. The transformation medium was prepared as follows: to a 2 L plastic beaker was added 20 g of dextrose, 5.0 g of yeast extract, 5.0 g of

soybean meal, 5.0 g of sodium chloride, 5.0 g of potassium phosphate (dibasic) and one L of deionized water, and the mixture was stirred at room temperature for 3 to 30 min. The pH of the mixture was then adjusted to 7.0 with 1 N HCl or 1 N NaOH. The resulting mixture was  
 5 dispensed into 500 mL flasks (100 mL per flask). The flasks were covered with Bio/Wrap and autoclaved at 121°C for 15 min. and cooled down to room temperature before use.

The culture was incubated at 28°C and 250 rpm for 3 days. One mL of the resulting  
 10 culture was added to a 500 mL flask containing 100 mL of the transformation medium and the flask was incubated at 28°C and 250 rpm for 24 hours. Ten mL of the resulting culture was transferred to a 50 mL flask, to which 1 mg of compound **331** in 0.2 mL ethanol was added. The flask was incubated at 28°C and 250 rpm for 23 hours. HPLC analysis showed that the peak area ratio of compound **459** to  
 15 compound **331** in the reaction culture was about 1.1/1.

#### Example 460

(1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-4-[2-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxyethyl]octahydro-  
 20 6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-1-naphthalenecarbonitrile (460)



Compound **231A** (2.00 g, 4.10 mmol) was dissolved in dichloromethane (40 mL) and cooled to 0°C. mCPBA (2.36 g, 8.20 mmol) was added. The reaction  
 25 mixture was then warmed up to room temperature and stirred under argon for 18 hours, followed by the addition of 10% Na<sub>2</sub>SO<sub>3</sub> (25 mL) and saturated NaHCO<sub>3</sub> (25 mL). After stirring for 20 minutes, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure

to give 2.0 g compound **460** as light yellow solid. HPLC: 99% at 4.00 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$   $[M+H] = 505.19$

5

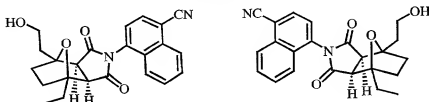
### Example 461

[3aR-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-Ethyl octahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile &

[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-Ethyl octahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitril (**461i** &

10

### 461ii)

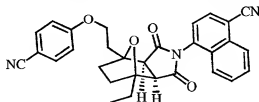


The racemic mixture of compounds **245C** was separated by normal  
15 phase preparative chiral HPLC using a Chiracel AD column (5 cm x 50  
cm), eluting with 20% solvent B (50% MeOH/EtOH) in solvent A  
(Heptane), flow rate: 50 mL/min. Compound **461i** eluted from 80 min to  
100 min and compound **461ii** eluted from 125 min to 150 min.

The absolute conformation for compounds **461i** and **461ii** was not  
20 determined. For simplicity in nomenclature, compound **461i** is designated  
herein as having an "R" configuration and compound **461ii** as having an  
"S" configuration. Enantiomerically pure products derived from compound  
**461i** are designated herein as having an "R" configuration and  
enantiomerically pure products derived from compound **461ii** are  
25 designated herein as having an "S" configuration.

**Example 462**

**[3aR-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (462)**



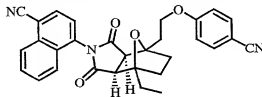
5

DBAD (29.5 mg, 0.128 mmol) was added to a solution of PPh<sub>3</sub> (33.6 mg, 0.128 mmol) in THF (0.5 mL). After stirring for 10 min, 4-cyanophenol (15.2 mg, 0.128 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound **461i** (18.3 mg, 0.047 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/hexane gave 16.9 mg (0.034 mmol, 73.2%) of compound **462**. HPLC conditions: 98% at 3.64 min (retention time) (YMC S5 ODS 4.6 X 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, detecting at 220 nm). MS (ES): m/z 492.23 [M+H]<sup>+</sup>.

20

**Example 463**

**[3aS-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (463)**



25

DBAD (29.5 mg, 0.128 mmol) was added to a solution of PPh<sub>3</sub> (33.6 mg, 0.128 mmol) in THF (0.5 mL). After stirring for 10 min, 4-cyanophenol (15.2 mg, 0.128 mmol) was added and the reaction mixture

- was stirred for an additional 5 min. Compound **461ii** (18.3 mg, 0.047 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/hexane gave 18.1 mg (0.037 mmol, 78.4%) of compound **463**. HPLC conditions: 97% at 3.63 min (retention time) (YMC S5 ODS 4.6 X 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2%  $H_3PO_4$ , detecting at 220 nm). MS (ES):  $m/z$  492.17  $[M+H]^+$ .

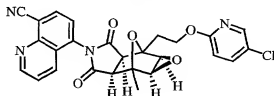
10

10024678-121901

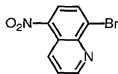
**Example 464**

**(1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-5-[2-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[1'isoindol-4-yl]-8-quinolinecarbonitrile**

**(464H)**

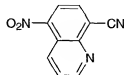


**A. 8-Bromo-5-nitro-quinoline (464A)**



8-Bromoquinoline (25.00 g, 120.2 mmol) was dissolved in sulfuric acid (82.5 mL) at rt and then cooled to 0°C. HNO<sub>3</sub> (fuming, 32.5 mL) was then slowly added over a 10 minute period. The reaction was then warmed to rt and then to 65°C. After 48 h at 65°C, the reaction was cooled to rt and poured onto 500 g of ice. This solution was extracted with methylene chloride (5 x 200 mL). The organic layers were washed once with brine and dried over anhydrous sodium sulfate. Concentration gave the crude compound **464A** as a light yellow solid (28.6 g, 94%). HPLC: 98% at 2.717 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

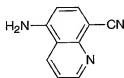
**B. 5-Nitro-quinoline-8-carbonitrile (464B)**



355

Compound **464A** (15.0 g, 59.3 mmol) was dissolved in DMF (120 mL) and zinc cyanide (4.20 g, 35.9 mmol) was added. Bis(diphenylphosphino)ferrocene (3.00 g, 5.40 mmol) and tris(benzylideneacetone)dipalladium (3.00 g, 3.30 mmol) were then added and the reaction was heated to 100°C for 1.5 h. The reaction was cooled to 22°C and then poured into concentrated ammonium hydroxide (900 mL) resulting in an orange precipitate which was filtered and rinsed with cold water (1 L). The resulting precipitate was dissolved in methylene chloride, washed with brine (1 x 300 mL) and then dried over anhydrous sodium sulfate. Concentration *in vacuo* gave the crude material as an orange solid which was purified by flash chromatography on silica gel eluting with methylene chloride to give 6.01 g (51%) of compound **464B** as a yellow solid. HPLC: 99% at 1.900 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**C. 5-Amino-quinoline-8-carbonitrile (464C)**

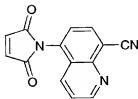


Compound **464B** (6.00 g, 30.1 mmol) was dissolved in THF (150 mL) at reflux with mechanical stirring. EtOH (150 mL) was then added followed by aqueous ammonium chloride (2.4 g/225 mL water). The mixture was heated at 70°C and then iron powder (325 mesh, 6.75 g, 120 mmol) was added with vigorous mechanical stirring. After 1 h, the reaction was cooled to 22°C and filtered through Celite rinsing with methylene chloride. The filtrate was then concentrated to ~250 mL and the pH was adjusted to 10 by addition of 1N NaOH. The solution was then extracted with ethyl acetate (5 x 150 mL). The combined organic layers were washed once with brine (250 mL) and then dried over anhydrous magnesium sulfate. Concentration *in vacuo* gave 5.09 g (100%) of compound **464C** as a yellow solid. HPLC: 99% at 1.143 min (retention



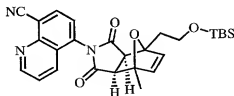
time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  170.16  $[M+H]^+$ .

**D. 5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-quinoline-8-carbonitrile (464D)**



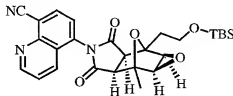
Compound **464C** (7.00 g, 41.4 mmol) and maleic anhydride (6.00 g, 62.1 mmol) were combined in a sealed tube and THF (10 mL) was added. The reaction mixture was heated to 115°C for 15 min then cooled to room temperature, resulting in the precipitation of the intermediate acid amide. The solid was filtered and rinsed with cold THF to give 11.0 g of the acid as a yellow solid. To the above acid amide was added  $Ac_2O$  (25 mL) in a sealed tube and the mixture was heated at 100°C for 15 min then cooled to room temperature. The resulting solid was filtered and rinsed with cold diethyl ether to give 8.30 g (80%) of compound **464D** as a yellow solid. HPLC: 97% at 1.783 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**E. (3 $\alpha$ , 4 $\beta$ , 7 $\beta$ , 7 $\alpha\alpha$ )-5-[4-[2-[[[1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (464E)**



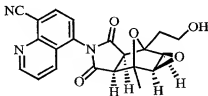
Compound **464D** (6.00 g, 24.1 mmol) was dissolved in a mixture of benzene (80 mL) and acetone (20 mL) followed by addition of compound **204A** (14.46 g, 60.15 mmol). The mixture was heated at 80°C for 14 h and then cooled to 22°C. Concentration *in vacuo* at 40°C followed by addition of acetone (40 mL) and concentration again at 40°C. The resulting yellow oil was purified by flash column chromatography on silica gel eluting with 0 – 10% acetone in chloroform to give 9.98 g (85%) of compound **464E** as a yellow oil. Compound **464E** was shown to be a single isomer by NMR spectroscopy. HPLC: 97% at 3.853 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 490.35 [M+H]<sup>+</sup>.

**F. (1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-5-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-8-quinolinecarbonitrile (**464F**)**



To a solution of compound **464E** (0.050 g, 0.10 mmol) in dichloromethane (2 mL) was added *m*CPBA (60% mixture, 0.063 g, 0.22 mmol). The reaction mixture was stirred at room temperature for 16 h and then additional dichloromethane (20 mL), saturated NaHCO<sub>3</sub> (10 mL) and 10% Na<sub>2</sub>SO<sub>3</sub> (10 mL) were added. The mixture was stirred vigorously for 40 min, the organic layer was then separated, washed once with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* gave 48 mg (96%) of compound **464F** as a light yellow solid. HPLC: 98% at 3.783 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 506.25 [M+H]<sup>+</sup>.

- G. (1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-5-[Octahydro-2-(2-hydroxyethyl)-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-8-quinolinecarbonitrile (**464G**)



Compound **464F** (1.30 g, 2.57 mmol) was dissolved in 2% conc. HCl/EtOH (50 mL). The reaction mixture was stirred at room temperature for 1 h and then saturated NaHCO<sub>3</sub> (50 mL) and dichloromethane (100 mL) were added. The organic layer was separated, washed once with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* gave 930 mg (93%) of compound **464G** as a yellow solid. HPLC: 98% at 1.863 (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 392.20 [M+H]<sup>+</sup>.

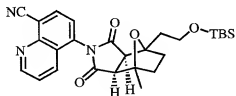
- H. (1 $\alpha$ , 2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-5-[2-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-6-methyl-3,5-dioxo-2,6-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-8-quinolinecarbonitrile (**464H**)

Triphenylphosphine (25 mg, 0.096 mmol) and DBAD (22 mg, 0.096 mmol) were mixed in THF (0.5 mL) under argon. After 5 min, 5-chloro-2-pyridinol (13 mg, 0.096 mmol) was added. The reaction mixture was stirred at 22°C for another 10 min, then compound **464G** (25 mg, 0.064 mmol) was added. The reaction mixture was stirred at 22°C under argon for 3 h, and then concentrated *in vacuo*. The crude material was purified by preparative TLC on silica gel eluting with 10% acetone in chloroform to give 11 mg (23%) of compound **464H** as a white solid. HPLC: 100% at 3.177 (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min

containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  503.14  $[M+H]^+$ .

#### Example 465

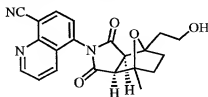
(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-5-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (465)



Compound **464E** (2.40 g, 4.91 mmol) was dissolved in ethyl acetate and Pd/C (10% Pd, 0.50 g) was added. Hydrogen was then introduced via a balloon. After 3 h, the reaction was purged with nitrogen and filtered through Celite, rinsing with ethyl acetate. Concentration *in vacuo* gave 2.39 g (99%) of compound **465** as a yellow oil. HPLC: 95% at 4.013 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  492.22  $[M+H]^+$ .

#### Example 466

(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (466)

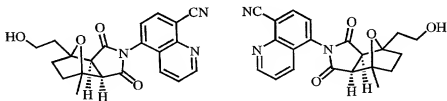


Compound **465** (1.40 g, 2.85 mmol) was dissolved in 2% conc. HCl/MeOH (20 mL) and stirred at 22°C for 3 h. The reaction was then concentrated to ~5 mL volume

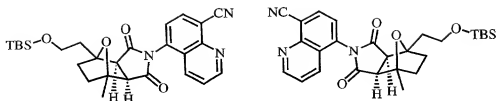
and quenched with a minimum amount of sat. aq. sodium bicarbonate. This solution was then extracted with methylene chloride (3 x 30 mL) and the combined organic layers were dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.893 g (93%) of compound **466** as a yellow solid. This material was taken on without further purification. HPLC: 98% at 2.140 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  378.25  $[M+H]^+$ .

#### Example 467

[3aR-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467Bi) & [3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467Bii)



- A. [3aR-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467Ai) & [3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[4-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467Aii)



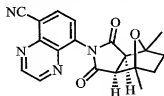
Compounds **465** was separated into its individual antipodes by normal phase preparative chiral HPLC. A Chiralcel OD column (50 x 500 mm) was used with a flow rate of 50 mL/min (16% EtOH/hexanes) monitoring at 220 nm. The faster eluting antipode compound **467Ai** had a retention time of 40.85 min (>99% ee) and the slower antipode compound **467Aii** had a retention time of 62.81 min (>99% ee). Both antipodes were isolated as white solids after separation. The absolute conformation for compounds **467Ai** & **467Aii** was not established. For simplicity in nomenclature, compound **467Ai** is designated herein as having an "R" configuration and compound **467Aii** as having an "S" configuration. Enantiomerically pure products derived from compound **467Ai** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **467Aii** are designated herein as having an "S" configuration.

- B.** [3a*R*-(3α,4β,7α)]-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (**467Bi**) & [3a*S*-(3α,4β,7α)]-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (**467Bii**)

Both antipodes were deprotected as described in example **464G** to give the corresponding alcohols, compounds **467Bi** and **467Bii** as white solids:

Compound **467Bi**: HPLC: 98% at 2.110 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  378.21 [M+H]<sup>+</sup>.

Compound **467Bii**: HPLC: 98% at 2.117 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  378.20 [M+H]<sup>+</sup>.

**Example 468****(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-8-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-5-quinoxalinecarbonitrile (468C)****A. 8-Nitro-quinoxaline-5-carbonitrile (468A)**

2,3-Diamino-4-nitro-benzonitrile (0.050 g, 0.28 mmol, as prepared in WO-98/32439) was added to solution of glyoxal (40% in water, 0.032 mL, 0.28 mmol) in acetic acid (0.75 mL) and stirred at 22°C for 3 h. The reaction was cooled to 0°C and water (2.0 mL) was added and the pH was adjusted to 9.0 by addition of ammonium hydroxide which caused the product to precipitate. The mixture was then filtered and rinsed with cold water. Drying *in vacuo* gave 0.039 g (70%) of compound **468A** as an orange solid. HPLC: 100% at 2.037 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**B. 8-Amino-quinoxaline-5-carbonitrile (468B)**

Compound **468A** (0.200 g, 1.00 mmol) was suspended in acetic acid (5.0 mL) and iron powder (325 mesh, 0.112 g, 2.00 mmol) was added. The reaction was then heated at 70°C for 20 min and then cooled to 22°C. The reaction was filtered through Celite, rinsing with ethyl acetate. The ethyl acetate rinse was collected and washed with sat. aq. K<sub>2</sub>CO<sub>3</sub>. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried over anhydrous magnesium sulfate. Concentration *in vacuo* gave 0.170 g (100%) of compound **468B** as a yellow solid. HPLC: 88% at 1.677 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 171.29 [M+H]<sup>+</sup>.

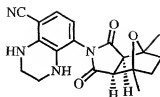
**C. (3α,4β,7β,7α)-8-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-5-quinoxalinecarbonitrile (468C)**

Compound **468B** (0.060 g, 0.35 mmol) was suspended in toluene (1.0 mL) with magnesium sulfate (0.060 g) and compound **20A** (0.104 g, 0.529 mmol). TEA (0.2 mL) was then added and the mixture was heated to 145°C in a sealed tube. After 16 h the reaction was cooled to 22°C and filtered through Celite, rinsing with acetone. The mixture was concentrated *in vacuo* and then purified by preparative TLC on silica gel eluting with 7% ethyl acetate/methylene chloride. This gave 0.018 g (15%) of compound **468C** as a yellow solid. HPLC: 100% at 2.040 and 2.133 min (atropisomers, retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 349.33 [M+H]<sup>+</sup>.

**Example 469**

**(3α,4β,7β,7α)-1,2,3,4-Tetrahydro-8-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-5-quinoxalinecarbonitrile (469B)**





**A. 8-Amino-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (469A)**



Compound **468A** (0.037 g, 0.18 mmol) was dissolved in a mixture of ethyl acetate (1.0 mL)/ethanol (1.0 mL) and 10% Pd/C (0.050 g) was added. Hydrogen was then introduced via a balloon. After 2 h, the reaction was purged with nitrogen and filtered through Celite, rinsing with ethyl acetate. Concentration *in vacuo* gave 0.029 g (90%) of compound **469A** as a red oil, which was taken on without further purification. HPLC: 97% at 3.217 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

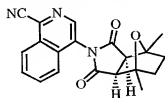
**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-1,2,3,4-Tetrahydro-8-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl)-5-quinoxalinecarbonitrile (469B)**

Compound **469A** (0.029 g, 0.17 mmol) was suspended in toluene (1.0 mL) with magnesium sulfate (0.030 g) and compound **20A** (0.050 g, 0.256 mmol). TEA (0.2 mL) was then added and the mixture was heated at 145°C in a sealed tube. After 48 h the reaction was cooled to 22°C and filtered through Celite, rinsing with acetone. The mixture was concentrated *in vacuo* and then purified by preparative TLC eluting with 20% acetone in chloroform. This gave 0.014 g (24%) of compound **469B** as a yellow

solid. HPLC: 85% at 2.267 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  353.19  $[M+H]^+$ .

### Example 470

#### (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-isoquinolinecarbonitrile (470E)



#### A. 4-Bromo-isoquinoline 2-oxide (470A)



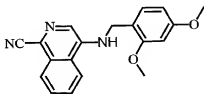
A solution of 4-bromoisoquinoline (4.16 g, 18.6 mmol) in 100 mL of chloroform was added dropwise over 1 h to a solution of 70% *m*CPBA (12.4 g, 50.3 mmol) in 100 mL of chloroform at room temperature. After stirring 18 h, the reaction mixture was washed with 1N NaOH (2 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford 4.23 g (94%) of compound **470A** as an off-white solid.  $^1\text{H}$  NMR-400 MHz ( $\text{CDCl}_3$ ):  $\delta$  8.71 (s, 1H), 8.43 (s, 1H), 8.09 (d, 1H,  $J = 8$  Hz), 7.70 (m, 3H).

#### B. 4-Bromo-isoquinoline-1-carbonitrile (470B)



1,8-Diazabicyclo[5.4.0]undec-7-ene (1.67 mL, 11.2 mmol) was added to a mixture of compound **470A** (1.12 g, 5.00 mmol) and cyanotrimethylsilane (0.75 mL, 5.5 mmol) in 35 mL of THF. The resulting homogeneous mixture was refluxed for 20 min. After concentrating *in vacuo*, the residue was purified by flash chromatography on a 5 x 15 cm silica gel column, eluting with 3:1 hexane:ethyl acetate to give 0.95 g (82%) of compound **470B** as a white powder.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.85 (s, 1H), 8.36 (d, 1H,  $J = 8.5$  Hz), 8.28 (d, 1H,  $J = 8.5$  Hz), 7.96 (t, 1H,  $J = 8.5$  Hz), 7.89 (t, 1H,  $J = 8.5$  Hz).

C. 4-(2,4-Dimethoxy-benzylamino)-isoquinoline-1-carbonitrile (**470C**)



A mixture of compound **470B** (699 mg, 3.00 mmol) and 2,4-dimethoxybenzylamine (4.8 mL, 30 mmol) in 15 mL of acetonitrile was refluxed for 16 h. After concentration *in vacuo*, the residue was purified on a 5 x 15 cm silica gel column, eluting with 3:2 hexane:ethyl acetate to afford 290 mg (30%) of **470C** as a light yellow solid. HPLC: 1.76 min (retention time) (Phenomenex C-18, 5 micron column, 4.6 x 30 mm, eluting with 10-90% aqueous methanol over 2 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm).

D. 4-Amino-isoquinoline-1-carbonitrile (**470D**)



Compound **470C** (50 mg, 0.16 mmol) was treated with trifluoroacetic acid (0.5 mL) for 1 h. The highly colored mixture was partitioned between ethyl acetate (30 mL)

and 1N NaOH (30 mL). After washing with brine (15 mL), the organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford 24 mg (92%) of compound **470D** as a yellow solid. HPLC: 99% at 1.09 min (retention time) (Phenomenex C-18, 5 micron column, 4.6 x 30 mm, eluting with 10-90% aqueous methanol over 2 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm). MS (ES<sup>+</sup>): m/z 170.2 [M+H]<sup>+</sup>.

An alternative route to the synthesis of compound **470D** is as follows. A mixture of compound **470B** (1.17 g, 5.02 mmol), benzophenone imine (1.05 mL, 6.26 mmol), palladium acetate (25 mg, 0.11 mmol), *rac*-2,2'-bis(diphenylphosphino)-1,1' binaphthyl (100 mg, 0.161 mmol) and cesium carbonate (2.30 g, 7.06 mmol) in 20 mL of toluene was heated at 100°C for 20 h. The reaction mixture was diluted with ethyl ether (200 mL) and filtered through Celite. After concentrating the filtrate, the residue was dissolved in 120 mL of THF and treated with 40 mL of 1N HCl. After standing for 2 h at room temperature, the mixture was partitioned between ethyl acetate (150 mL) and 0.25 N NaOH (160 mL). After washing with brine (100 mL), the organic layer was dried over magnesium sulfate. The organic layer was filtered and ~ 50 g of celite was added to the filtrate. After concentration *in vacuo*, the powdery residue was purified by flash chromatography on a 5 x 15 cm silica gel column eluting with 1 L each of 1:1 ethyl acetate:hexane, 6:4 ethyl acetate:hexane and 8:2 ethyl acetate:hexane to give 450 mg (53%) of **470D** as a yellow powder.

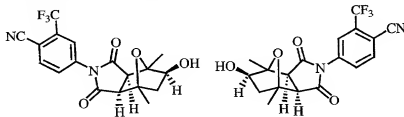
**E. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-isoquinolinecarbonitrile (470E)**

A mixture of compound **470D** (24 mg, 0.14 mmol), compound **20A** (55 mg, 0.28 mmol), triethylamine (0.1 mL), magnesium sulfate (100 mg), 2-methoxyethylether (0.5 mL) and DMF (0.1 mL) was heated in a sealed vessel to 250°C for a total of 2.5 h using a microwave heating device. After partitioning the reaction mixture between ethyl acetate (25 mL) and water (25 mL), the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. Approximately half of the residue was purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 50 mm, eluting with 10-100% aqueous methanol

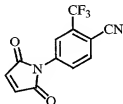
over 10 min containing 0.1% TFA, 20 mL/min). Concentration of the pure fraction afforded 6 mg (12%) of compound **470E** as a white powder. HPLC: 99% at 1.42 min (retention time) (Phenomenex C-18, 5 micron column, 4.6 x 30 mm, eluting with 10-90% aqueous methanol over 2 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm). MS ( $ES^+$ ):  $m/z$  348.23  $[M]^+$ .

### Example 471

[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471Di) & [3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471Dii)



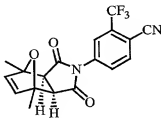
#### A. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile (471A)



A mixture of 3-trifluoromethyl-4-cyano-aniline (24.0 g, 129 mmol) and maleic anhydride (14.0 g, 143 mmol) in 50 mL of acetic acid was heated at 115°C overnight. A precipitate was obtained during the heating period. The reaction was allowed to stand at rt for an additional overnight period. The solid was removed by filtration, the filter cake was washed with diethyl ether and dried to give 21 g (79 mmol, 61%) of compound **471A** as an off white solid. HPLC: 100% at 2.11 min (retention time) (YMC S5 ODS column,

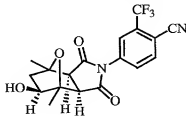
4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

- B.** (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (**471B**)



A suspension of compound **471A** (13.0 g, 48.8 mmol) and 2,5-dimethylfuran (10.5 mL, 98.6 mmol) in 50 mL of toluene was heated at 60°C, under argon. A solution was obtained on initial heating and a precipitate was observed after approximately 1 h. Heating was continued overnight. After cooling to rt, the suspension was allowed to stand at 4°C overnight. The resulting solid was filtered and the filter cake was washed with cold toluene followed by air drying to give 13.2 g of pure compound **471B** as a white solid. The filtrate volume was reduced *in vacuo* by one half and the resulting solution was treated as above to yield an additional 2.8 g of pure compound **471B** (total 16.0 g, 90%). HPLC: 90% at 3.65 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

- C.** (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (**471C**)



A solution of compound **471B** (25 g, 69 mmol) in 125 mL of THF, in a dry flask under nitrogen, was cooled to 10°C with an ice bath. To this solution was added neat borane-dimethylsulfide complex (13.0 mL, 138 mmol) dropwise over 10 min, while maintaining a reaction temperature of <15°C. The reaction mixture was stirred for 30 min at rt and then in an ice bath cooled to 10°C. To the cool solution was slowly added 480 mL of pH 7 phosphate buffer, which resulted in a strong exothermic reaction and vigorous gas evolution. The solution was maintained at <21°C throughout the addition by means of an ice bath. To the resulting solution was added 240 mL of ethanol and the resulting mixture was cooled to 5°C with an ice bath. To the cooled solution was added 50 mL of 30% hydrogen peroxide and the resulting mixture was stirred at 10-20°C for 1.5 h. The mixture was extracted with ethyl acetate (2 x 1 L) and the combined organic layers were washed with 10% sodium sulfite (1 x 500 mL) and brine (2 x 300 mL) and dried over MgSO<sub>4</sub>. Concentration *in vacuo* afforded 29 g of crude product as a white solid. This material was subjected to flash chromatography on a 1.2 L column of silica gel equilibrated with 100% CH<sub>2</sub>Cl<sub>2</sub>. The material was applied to the column as a solution consisting of 100 mL EtOAc (warm) and 400 mL CH<sub>2</sub>Cl<sub>2</sub>. Initial elution with CH<sub>2</sub>Cl<sub>2</sub> (3 L), followed by 25% EtOAc/75% CH<sub>2</sub>Cl<sub>2</sub> (3 L) and finally 50% EtOAc/50% CH<sub>2</sub>Cl<sub>2</sub> (6 L) gave 11.8 g (45%) of compound **471C** which is a racemic mixture.

Alternatively compound **471C** can be made by the following approach: A dry flask containing compound **471B** (8.90 g, 24.6 mmol) and Wilkinson's catalyst (0.57 mg, 0.62 mmol) was degassed 4x with vacuum/argon. THF (40 mL) was added to the flask and the mixture was stirred until a clear brown solution was obtained. Catecholborane (49 mL, 49 mmol, 1 M in THF) was then added dropwise over 20 min and a slight exotherm was observed. Stirring was continued for 45 min followed by cooling of the reaction mixture with an ice bath. pH 7 phosphate buffer (175 mL) was slowly added, followed by the consecutive addition of ethanol (87 mL) and 30% hydrogen peroxide (18 mL). Stirring was continued with cooling and the reaction progress was monitored by HPLC for 4 h. The reaction was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 250 mL). The combined extracts were washed with 1:1 1N NaOH:15% sodium sulfite (300 mL) and brine, dried over MgSO<sub>4</sub>, and the solvent was removed *in vacuo* to afford 8.5 g of a tan solid. The

crude product was subjected to flash chromatography on a 500 cm<sup>3</sup> silica gel column eluting with a gradient of 25-50% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> to give 6.00 g compound **471C** (15.8 mmol, 64%) as a white solid. HPLC: 90% at 2.45 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 [M+H]<sup>+</sup>.

- D. [3aR-(3α,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (**471Di**) & [3aS-(3α,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (**471Dii**)

The individual antipodes of compound **471C** were separated by normal phase preparative chiral HPLC (CHIRALPAK AD, 5 x 50 cm column). A 2.5 g portion of **471C** was dissolved into 25 mL of warm acetone and diluted to 50-75 mL with hexane for injection. Isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 50 mL/min gave the faster eluting compound **471Di** (Chiral HPLC: 10.02 min; CHIRALPAK AD 4.6 x 250 mm column; isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting compound **471Dii** (Chiral HPLC: 14.74 min; CHIRALPAK AD 4.6 x 250 mm column; isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). Compounds **471Di** & **471Dii**: HPLC: 90% at 2.45 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 [M+H]<sup>+</sup>. The absolute stereochemistry of compounds **471Di** & **471Dii** was determined by single crystal X-ray diffraction studies and is as described by the designated nomenclature.

The resulting HPLC purified fractions of compounds **471Di** & **471Dii** were further purified by crystallization using any one of the procedures described below.

- 1) From Ethyl Acetate



A 700 mg portion of compound **471Di**, obtained after chiral chromatography as described above, was dissolved in ethyl acetate (10 mL) at rt. The solution was diluted with small portions of hexane (20 mL) until cloudiness was observed. The solution was allowed to stand overnight at rt. The resulting white solid was filtered and air dried to afford 430 mg of compound **471Di** as a white powder. This sample was further dried at 60°C (3 h, 0.5 Torr), then at 70°C, (12 h, 0.5 Torr).

2) From Acetone

A 500 mg portion of compound **471Di**, obtained after chiral chromatography as described above, was dissolved in a minimal amount of acetone (3 mL) and slowly diluted with hexane (1 mL). The clear colorless solution was allowed to stand overnight at rt. The resulting white solid was filtered and air dried to afford 440 mg of compound **471Di** as a white powder. This sample was further dried at 60°C, (3 h, 0.5 Torr) then at 70°C, (12 h, 0.5 Torr).

3) From Methanol

A 500 mg portion of compound **471Di**, obtained after chiral chromatography as described above, was dissolved in 5 mL of hot (steam bath) methanol. The clear colorless solution was allowed to stand at rt for 2 h, then at 4°C overnight. The resulting solid was filtered, washed with minimal cold methanol and air dried for to afford 360 mg of compound **471Di** as a white powder. This sample was further dried at 70°C, (12 h, 0.5 Torr).

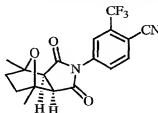
4) From CH<sub>2</sub>Cl<sub>2</sub>

A 7.00 g portion of compound **471Di**, obtained after chiral chromatography as described above, was dissolved in 75 mL of CH<sub>2</sub>Cl<sub>2</sub> at rt. The clear and colorless solution was slowly diluted with hexane (48 mL) until crystallization was observed.

The solution was allowed to stand at rt for 1 h, then at 4°C overnight. The resulting crystalline material was filtered and then washed with a minimal amount of cold 2:1 CH<sub>2</sub>Cl<sub>2</sub>:hexane. The large crystals were ground to a fine powder and dried at 50°C (12 h, 0.5 Torr) to yield 5.96 g of compound **471Di** as a white powder

#### Example 472

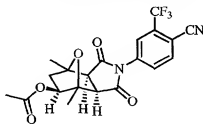
**(3α,4β,7β,7α)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (472)**



A solution of compound **471B** (500 mg, 1.38 mmol) in ethyl acetate (10 mL), containing 10% Pd/C (25 mg, cat.) was stirred at rt under an atmosphere of hydrogen introduced via a balloon. After 2 h the reaction was filtered through Celite and the filter cake was washed with EtOAc. The clear, colorless filtrate was concentrated *in vacuo* to yield 501 mg (1.38 mmol, 100%) of compound **472** as a white solid. No further purification was required. HPLC: 99% at 3.04 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): *m/z* 382.2 [M+NH<sub>4</sub>]<sup>+</sup>.

#### Example 473

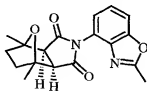
**(3α,4β,5β,7β,7α)-4-[5-(Acetyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (473)**



To a solution of compound **471C** (1.50 g, 3.95 mmol) in 10 mL of pyridine, cooled to 0°C under argon, was added acetic anhydride (0.42 mL, 4.4 mmol) dropwise, followed by DMAP (5 mg, 0.04 mmol). Stirring was continued at rt for 4 h. The solution was concentrated *in vacuo* and the resulting residue was diluted with ethyl acetate, and washed consecutively with 1N HCl (2x), brine (2x), sat. NaHCO<sub>3</sub>, and brine (2x). The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The resulting solid was dried at 60°C (20 h, 0.5 Torr) to yield 1.55 g (3.67 mmol, 93%) of compound **473** as a white crystalline solid. HPLC: 99% at 2.10 min (retention time) (Phenomenex Luna C18 column, 2 x 30 mm, 0-100% aqueous acetonitrile over 3 min containing 10 mM NH<sub>4</sub>OAc at 1 mL/min, monitoring at 220 nm). MS (ESI): m/z 421.4 [M-H]<sup>-</sup>.

#### Example 474

#### (3ac,4ß,7ß,7ac)-Hexahydro-4,7-dimethyl-2-(2-methyl-4-benzoxazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (474F)



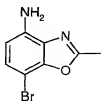
#### A. 2-Methyl-4-nitrobenzoxazole (474A)



To 2-amino-3-nitrophenol (6.17 g, 40.0 mmol) was added triethylorthoacetate (25.96 g, 160.0 mmol) and the mixture was heated at 100°C for 12 h to give a dark red solution. Cooling to room temperature produced a crystalline mass which was filtered and washed with hexane to give compound **474A** (6.78 g, 95%) as light maroon needles. HPLC: 98.1% at 1.86 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 179.08 [M+H]<sup>+</sup>.

**B. 4-Amino-2-methylbenzoxazole (474B)**

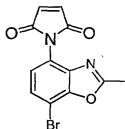
Compound **474A** (6.78 g, 38.1 mmol) was dissolved in a 1:1 mixture of 10% acetic acid/ethyl acetate (100 mL total volume) and heated to 65°C. Iron powder (10.63 g, 190.2 mmol) was added portionwise. After stirring for 3 h, TLC indicated complete consumption of starting material. The cooled reaction mixture was filtered through a pad of Celite and the pad was washed with 50 mL of ethyl acetate. The organic layer was separated, washed with water (2 x 25 mL), brine (1 x 25 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 25% ether/CH<sub>2</sub>Cl<sub>2</sub> to give 3.90 g (69%) of compound **474B** as a light brown solid. HPLC: 95.8% at 2.43 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 149.11 [M+H]<sup>+</sup>.

**C. 4-Amino-7-bromo-2-methylbenzoxazole (474C)**

Compound **474B** (3.90 g, 26.3 mmol) was dissolved in DMF (45 mL) and cooled to -5°C and *N*-bromosuccinimide (4.68 g, 26.3 mmol) was added in small portions and the reaction stirred for 5 h. The mixture was poured into 150 mL of ice water to give a cream colored solid which was filtered, washed with water, dissolved in CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification of the crude material by flash chromatography on silica gel eluting with 20% ether/CH<sub>2</sub>Cl<sub>2</sub> gave compound **474C**

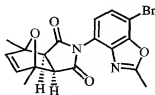
(3.36 g, 56%) as a beige solid. HPLC: 95.4% at 2.583 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  228.03  $[M+H]^+$ .

**D. 1-(7-Bromo-2-methyl-benzoxazol-4-yl)-pyrrole-2,5-dione (474D)**



Compound **474C** (1.40 g, 6.17 mmol) was dissolved in 20 mL of acetic acid, maleic anhydride (0.635 g, 6.47 mmol) was added and the reaction was heated at reflux under nitrogen for 5 h. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with 10% ether/ $CH_2Cl_2$  to give compound **474D** (1.73 g, 91%) as a pale yellow solid. HPLC: 93.6% at 1.36 min. (Phenomenex column, 30 x 4.6 mm, 10-90% aqueous methanol over 2 min containing 0.1% TFA, 5 mL/min, monitoring at 220 nm. MS (ES):  $m/z$  308.02  $[M+H]^+$ .

**E. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Bromo-2-methyl-4-benzoxazolyl)-3a,4,7,7a-tetrahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (474E)**



Compound **474D** (0.307 g, 1.00 mmol) was dissolved in benzene (2 mL) and 2,5-dimethylfuran (0.154 g, 1.60 mmol) was added via syringe. The reaction mixture was heated to 60°C for 12 h. The cooled reaction mixture was concentrated *in vacuo* at 40°C

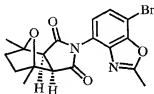
to give compound **474E** as an off-white foam which was used directly in the next reaction without purification.

**F. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-(2-methyl-4-benzoxazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (474F)**

Compound **474E** (0.403 g, 1.00 mmol) was dissolved in EtOH/EtOAc (4 mL/4 mL) and 10% Pd/C (100 mg) was added. The reaction mixture was stirred at room temperature for 6 h under an atmosphere of H<sub>2</sub> supplied by a balloon and then filtered through Celite. Concentration of the filtrate *in vacuo* gave a brown solid. Purification by flash chromatography on silica gel eluting with 10% acetone/CHCl<sub>3</sub> (250 mL), 15% acetone/CHCl<sub>3</sub> (250 mL), and 20% acetone/CHCl<sub>3</sub> (250 mL) gave compound **474F** (0.089 g, 27%) as a white foam. HPLC: 91% at 2.28 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 328.34 [M+H]<sup>+</sup>.

**Example 475**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(7-Bromo-2-methyl-4-benzoxazolyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (475)**

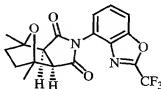


Compound **474E** (0.202 g, 0.501 mmol) was dissolved in 1/1 EtOAc/EtOH (10 mL) and 10% Pt/C (100 mg) was added. The reaction mixture was stirred at room temperature under an H<sub>2</sub> balloon for 6 h. The reaction was filtered through Celite and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 10% ether/CH<sub>2</sub>Cl<sub>2</sub> gave 0.063 g (31%) of compound **475** as a colorless oil which

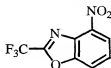
solidified upon standing to give a white solid. HPLC: 92.5% at 2.83 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  406.21  $[M+H]^+$ .

### Example 476

#### (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-[2-(trifluoromethyl)-4-benzoxazolyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (476D)

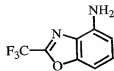


#### A. 4-Nitro-2-trifluoromethylbenzoxazole (476A)



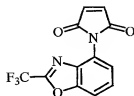
2-Amino-3-nitrophenol (10.00 g, 64.88 mmol) was added to 100 mL of vigorously stirring trifluoroacetic anhydride and the resulting mixture was stirred at room temperature for 12 h. The solvent was removed *in vacuo* to give a dark blue solid which was dissolved in 200 mL of  $CH_2Cl_2$  and washed sequentially with 10% NaOH (2 x 100 mL), water (100 mL), brine (100 mL), and dried over  $MgSO_4$ . Filtration and concentration *in vacuo* gave compound **476A** (10.78 g, 72%) as a brown solid. No further purification was required. HPLC: 92.9% at 2.43 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

#### B. 4-Amino-2-trifluoromethylbenzoxazole (476B)



Compound **476A** (10.75 g, 46.30 mmol) was dissolved in 1:1 EtOAc/10% HOAc (250 mL) and heated to 65°C. Iron powder (12.93 g, 231.5 mmol) was added portionwise and the reaction was stirred for 6 h at 65°C. After cooling, the mixture was filtered through Celite rinsing with EtOAc. The organic layer was separated, washed with H<sub>2</sub>O (3 x 100 mL), brine (100 mL), dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give a brown oil. The crude material was purified by flash chromatography on silica gel eluting with 70/30 CH<sub>2</sub>Cl<sub>2</sub>/hexanes to give compound **476B** (7.02 g, 75%) as a yellow crystalline solid. HPLC: 96.7% at 2.68 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. 1-(2-Trifluoromethyl-benzoxazol-4-yl)-pyrrole-2,5-dione (**476C**)



Compound **476B** (0.500 g, 2.48 mmol) was dissolved in acetic acid (10 mL) and maleic anhydride (0.267 g, 2.72 mmol) was added. The mixture was heated at reflux for 3 h, cooled and the solvent removed *in vacuo* to give a tan solid. The crude product was purified by flash chromatography on silica gel eluting with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to give compound **476C** (0.40 g, 57%) as an off-white solid. HPLC: 89.7% at 2.38 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 283.21 [M+H]<sup>+</sup>.

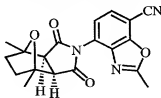


**D. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-[2-(trifluoromethyl)-4-benzoxazolyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (476D)**

Compound **476C** (0.24 g, 0.85 mmol) and 2,5-dimethylfuran (0.132 g, 1.37 mmol) were combined in 3 mL of benzene in a sealed tube and heated at 60°C for 12 h. The mixture was cooled and concentrated *in vacuo* to give a yellow oil which was dissolved in 1/1 EtOAc/EtOH (6 mL). 10% Pd/C (100 mg) was added and the mixture was stirred under an H<sub>2</sub> balloon for 3.5 h. The reaction was filtered through Celite and the solvent removed *in vacuo* to give the crude product as a pale yellow oil. Purification by flash chromatography on silica gel eluting with 2% Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> gave 0.107 g (33%) of compound **476D** as a white foam. HPLC: 96.5% at 2.80 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 381.17 [M+H]<sup>+</sup>.

**Example 477**

**(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-Methyl-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-7-benzoxazolecarbonitrile (477E)**



**A. 2-Cyano-5-nitrophenol (477A)**



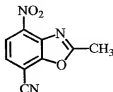
3,4-Methylenedioxy nitrobenzene (1.67 g, 10.0 mmol) was dissolved in 20 mL of HMPA and sodium cyanide (0.49 g, 10.0 mmol) was added. The reaction was heated to 150°C under nitrogen and three portions of sodium cyanide (0.245 g, 5.00 mmol, total) were added over 15 min. The reaction was maintained at 150°C for 45 min, cooled, and poured into 50 mL of H<sub>2</sub>O followed by the addition of 50 mL of 5% NaOH. The aqueous layer was extracted with ether (2 x 25 mL) and the organic layer was discarded. The basic aqueous layer was carefully acidified to pH 4 by addition of 10% HCl and extracted with ether (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> gave 1.05 g (64%) of compound **477A** as a yellow-brown solid. HPLC: 91.6% at 1.03 min (retention time) (Phenomenex column, 30 x 4.6 mm, 10-90% aqueous methanol over 2 min containing 0.1% TFA, 5 mL/min, monitoring at 220 nm. MS (ES): m/z 165.23 [M+H]<sup>+</sup>.

**B. 2-Amino-4-cyano-3-hydroxynitrobenzene (477B)**



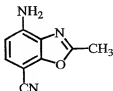
Compound **477A** (0.438 g, 2.67 mmol) was dissolved in 25 mL of DMSO and trimethylhydrazinium iodide (0.534 g, 2.67 mmol) was added. Sodium pentoxide (0.880 g, 8.01 mmol) was added under N<sub>2</sub> to give a deep red solution and stirring was continued overnight at rt. The reaction mixture was poured into 50 mL of 10% HCl and extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried over sodium sulfate and concentrated *in vacuo* to give compound **477B** as an oily red solid which was used directly in the next reaction without further purification.

## C. 7-Cyano-2-methyl-4-nitrobenzoxazole (477C)



Compound **477B** (0.360 g, 2.01 mmol) and triethyl orthoacetate (1.30 g, 8.04 mmol) were combined and heated at reflux under nitrogen for 1 h. The solvent was removed *in vacuo* and the resulting residue purified by flash chromatography eluting with 5% ether/CH<sub>2</sub>Cl<sub>2</sub> to give 0.255 g (63%) of compound **477C** as a brown solid. HPLC: 98.4% at 1.80 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 204.28 [M+H]<sup>+</sup>.

## D. 4-Amino-7-cyano-2-methylbenzoxazole (477D)



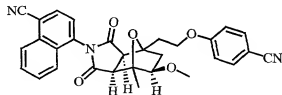
Compound **477C** (0.156 g, 0.77 mmol) was dissolved in a 1:1 mixture of EtOAc/10% HOAc (20 mL) and heated to 65°C. Iron powder (325 mesh, 0.214 g, 3.83 mmol) was added and the reaction was stirred for 4 h. The cooled mixture was filtered through Celite and the resulting filtrate was washed with water (25 mL), brine (25 mL), dried over MgSO<sub>4</sub>, and concentrated to give compound **477D** (0.118 g, 89%) as an orange solid. HPLC: 87% at 2.03 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 174.05 [M+H]<sup>+</sup>.

E. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-Methyl-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-7-benzoxazolecarbonitrile (477E)

Compound **477D** (0.060 g, 0.35 mmol) and compound **20A** (0.071 g, 0.37 mmol) were combined in a sealed tube with toluene (2 mL), triethylamine (0.24 mL, 1.7 mmol), and  $\text{MgSO}_4$  (0.104 g, 0.866 mmol). The sealed tube was heated at 135°C for two days. The cooled reaction mixture was diluted with EtOAc, filtered, and concentrated *in vacuo* to give crude product as a brown oil. Purification by flash chromatography on silica gel eluting with 1/1 EtOAc/hexanes gave 0.014 g (12%) of compound **477E** as an off-white solid. HPLC: 96.5% at 2.27 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  352.23  $[\text{M}+\text{H}]^+$ .

#### Example 478

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, slow eluting enantiomer (**478**)

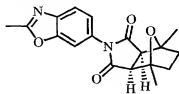


*n*-BuLi (0.050 mL, 1.6 M, 0.075 mmol) was added to a solution of compound **244ii** (33.7 mg, 0.0683 mmol) in THF (1.0 mL) at -78°C under argon. The reaction mixture was warmed to room temperature and methyl fluorosulfonate (0.010 mL, 0.12 mmol) was added dropwise. Once starting material was consumed, as was evident by HPLC, the reaction was quenched with  $\text{H}_2\text{O}$  and the resulting aqueous mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by reverse phase preparative HPLC [22.09 min (YMC S5 ODS column, 20 x 100 mm, 0-100% aqueous methanol over 25 min containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 13.0 mg (38%) of compound **478** as a white solid. HPLC: 93% at 3.35 min (YMC S5 ODS

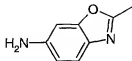
column, 4.6 x 50 mm, 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  508.17  $[M+H]^+$ .

### Example 479

#### (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-(2-methyl-6-benzoxazolyl)-4,7-epoxy-1H-isindole-1,3(2H)-dione (479B)



#### A. 2-Methyl-6-aminobenzoxazole (479A)



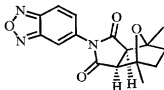
To a solution of 2-methyl-6-nitrobenzoxazole (100 mg, 0.560 mmol) in AcOH (2 mL) was added iron powder (325 mesh, 63.0 mg, 1.12 mmol) at 70°C in a single portion. After 15 min at 70°C additional iron powder (325 mesh, 63.0 mg, 1.12 mmol) was added and stirring was continued for 15 min. The mixture was cooled and concentrated under reduced pressure. The resulting residue was taken up into EtOAc and washed with sat.  $\text{Na}_2\text{CO}_3$  followed by  $\text{H}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$ , concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with a gradient of 0 to 25% EtOAc in  $\text{CH}_2\text{Cl}_2$  to yield 69 mg (83%) of compound **479A** as a solid. HPLC: 97% at 0.24 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2%  $\text{H}_3\text{PO}_4$ , 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  149.2  $[M+H]^+$ .

#### B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-(2-methyl-6-benzoxazolyl)-4,7-epoxy-1H-isindole-1,3(2H)-dione (479B)

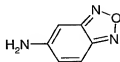
Compound **479A** (30 mg, 0.20 mmol),  $\text{MgSO}_4$  (60 mg, 0.50 mmol), triethylamine (140  $\mu\text{L}$ , 1.00 mmol) and compound **20A** (45 mg, 0.23 mmol) were taken up in 0.25 mL of toluene and placed in a sealed tube. The sealed tube was heated at  $135^\circ\text{C}$  for 14 h and the reaction was allowed to cool to rt. The mixture was filtered through a short pad of Celite, eluting with MeOH and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 50% EtOAc in  $\text{CH}_2\text{Cl}_2$  to give 49 mg (65%) of compound **479B** as a tan solid. HPLC: 98% at 2.30 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  326.9  $[\text{M}+\text{H}]^+$ .

#### Example 480

(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2,1,3-Benzoxadiazol-5-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (480B)



#### A. 5-Amino-2,1,3-benzoxadiazole (480A)



To a solution of 2,1,3-benzoxadiazole-5-carboxylic acid (102 mg, 0.621 mmol) in THF (3 mL) was added triethylamine (103  $\mu\text{L}$ , 0.739 mmol) followed by DPPA (160  $\mu\text{L}$ , 0.739 mmol) at room temperature. The mixture was stirred for 4 h, diluted with  $\text{CH}_2\text{Cl}_2$  and washed with water. The organic layer was dried over  $\text{MgSO}_4$ , concentrated and

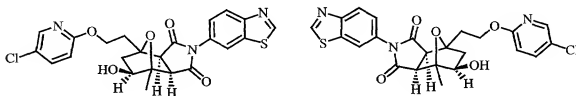
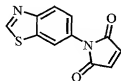
purified by flash chromatography on silica gel with 0 to 50% EtOAc in  $\text{CH}_2\text{Cl}_2$ . The resulting material was dissolved in AcOH (2 mL) and water (0.7 mL) was added dropwise yielding a slightly cloudy solution which was heated at  $105^\circ\text{C}$  for 30 min. The mixture was cooled, made basic with sat.  $\text{Na}_2\text{CO}_3$  solution and extracted several times with THF. The combined organic layers were dried over  $\text{MgSO}_4$ , concentrated and purified by flash chromatography on silica gel eluting with 0 to 15% MeOH in  $\text{CH}_2\text{Cl}_2$  to give 34 mg (41%) of compound **480A** as a yellow solid. HPLC: 100% at 1.27 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2%  $\text{H}_3\text{PO}_4$ , 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  136.0  $[\text{M}+\text{H}]^+$ .

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(2,1,3-Benzoxadiazol-5-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (480B)**

Compound **480A** (34 mg, 0.25 mmol),  $\text{MgSO}_4$  (76 mg, 0.63 mmol), triethylamine (180  $\mu\text{L}$ , 1.26 mmol) and compound **20A** (74 mg, 0.38 mmol) were dissolved in 0.25 mL of toluene and placed in a sealed tube. The sealed tube was heated at  $135^\circ\text{C}$  for 14 h. The cooled reaction mixture was filtered through a short pad of Celite, eluting with acetone and the solvent was removed *in vacuo*. The residue was purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm, eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min). Concentration of the desired fractions afforded a residue which was partitioned between  $\text{CH}_2\text{Cl}_2$  and sat.  $\text{NaHCO}_3$  solution. The aqueous layer was extracted once with  $\text{CH}_2\text{Cl}_2$  and the combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ . Concentration under reduced pressure gave 42 mg (53%) of compound **480B** as a yellow solid. HPLC: 100% at 2.62 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.91 (d, 1H), 7.90 (dd, 1H), 7.37 (dd, 1H), 3.09 (s, 2H), 1.85 (s, 4H), 1.67 (s, 6H).

**Example 481**

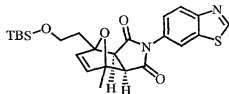
[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-2-pyridinyloxy)ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481D) & [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-2-pyridinyloxy)ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481E)]

**A. 1-Benzothiazol-6-yl-pyrrole-2,5-dione (481A)**

A mixture of 5-aminobenzothiazole (2.00 g, 13.3 mmol) and maleic anhydride (1.96 g, 20.0 mmol) in AcOH (27 mL) was heated at 115°C for 20 h. The mixture was cooled and concentrated under reduced pressure. The residue was taken up in THF and washed with saturated Na<sub>2</sub>CO<sub>3</sub>. The aqueous layer was extracted several times with THF and the combined organic layers were dried over MgSO<sub>4</sub>. Purification by flash chromatography on silica gel eluting with 0 to 50% EtOAc in CH<sub>2</sub>Cl<sub>2</sub> gave 1.37 g (45%) of compound **481A** as a pale yellow solid. HPLC: 100% at 2.62 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 231.0 [M+H]<sup>+</sup>.

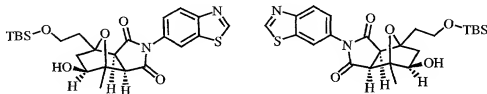


- B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-2-(6-Benzothiazolyl)-4-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-3a,4,7,7a-tetrahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481B)



A suspension of compound **481A** (445 mg, 1.93 mmol) and compound **204A** (929 mg, 3.87 mmol) in benzene (2 mL) was heated to 60°C and acetone was added until a clear solution was obtained. The resulting mixture was stirred at 60°C for 24 h and was then slowly concentrated *in vacuo*. The resulting residue was dissolved in acetone and slowly concentrated *in vacuo*. This process was repeated a total of three times. Purification by flash chromatography on silica gel eluting with 0 to 30% acetone in hexanes gave 820 mg (90%) of compound **481B** as a white solid. HPLC: 100% at 2.62 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  471.3  $[M+H]^+$ .

- C. [3a*R*-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-2-(6-Benzothiazolyl)-7-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481Ci) & [3a*S*-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-2-(6-Benzothiazolyl)-7-[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481Cii)



To a solution of compound **481B** (75 mg, 0.16 mmol) in THF (1 mL) was added Wilkinson's catalyst (32 mg, 0.030 mmol) and catecholborane (1.0 M in THF, 1.6 mL, 1.6 mmol) at room temperature under nitrogen. The resulting mixture was stirred for 2.5 h before it was cooled to 0°C. EtOH (5 mL), 3 N NaOH (2 mL) and H<sub>2</sub>O<sub>2</sub> (30%, 1 mL) were added sequentially, and the mixture was stirred for 2 h at 0°C. The reaction was quenched by the addition of cold 10% Na<sub>2</sub>SO<sub>3</sub> solution (excess) followed by water. The aqueous layer was extracted several times with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure followed by purification by flash chromatography on silica gel eluting with 0 to 100% EtOAc in hexanes gave 13 mg (17%) of a racemic mixture of compounds **481Ci** & **481Cii** as a tan solid. HPLC: 96% at 3.58 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H<sub>3</sub>PO<sub>4</sub>, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 489.3 [M+H]<sup>+</sup>. The racemic mixture was separated into its individual enantiomers by normal phase preparative chiral HPLC (CHIRALPAK AD 5 x 50 cm column; eluting with 20% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min) to give the faster eluting enantiomer, compound **481Ci**: (Chiral HPLC: 9.40 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting enantiomer, compound **481Cii**: (Chiral HPLC: 10.47 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). The absolute conformation for compounds **481Ci** & **481Cii** was not established. For simplicity in nomenclature, compound **481Ci** is designated herein as having an "R" configuration and compound **481Cii** as having an "S" configuration. Enantiomerically pure products derived from compound **481Ci** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **481Cii** are designated herein as having an "S" configuration.

- D. [3a*R*-(3α,4β,5β,7β,7α)]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1*H*-isoindole-1,3(2*H*)-dione (**481D**)

Compound **481Ci** (84 mg, 0.17 mmol) was suspended into EtOH (2 mL) and conc. HCl (40  $\mu$ L) was added at room temperature. The mixture was stirred for 15 min before several drops of sat. NaHCO<sub>3</sub> solution were added. Concentration under reduced pressure yielded a residue which was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and sat. NaHCO<sub>3</sub> solution. The aqueous layer was extracted several times with CH<sub>2</sub>Cl<sub>2</sub> and finally with EtOAc. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified by preparative TLC eluting with 50% acetone in CHCl<sub>3</sub>. This procedure served to remove the TBS group from compound **481Ci**, yielding the free primary alcohol. A 12 mg (0.03 mmol) portion of the free alcohol of compound **481Ci** was reacted with 5-chloro-2-pyridinol (8 mg, 0.06 mmol), PPh<sub>3</sub> (17 mg, 0.060 mmol) and di-*tert*-butylazodicarboxylate (15 mg, 0.060 mmol) in THF (0.5 mL) according to the general procedure described in Example **244**. The mixture was stirred for 24 h at room temperature, diluted with 1N NaOH and the aqueous layer was extracted several times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified by preparative TLC, eluting with 25% acetone in CHCl<sub>3</sub> to give 9 mg (58%) compound **481D** as a white solid. HPLC: 98% at 2.94 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H<sub>3</sub>PO<sub>4</sub>, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 486.2 [M+H]<sup>+</sup>.

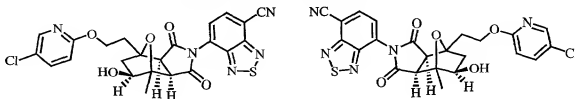
**E. [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (**481E**)**

As described in Example **481D**, compound **481Cii** (58 mg, 0.12 mmol) was treated with EtOH (2 mL) containing 12 N HCl (40  $\mu$ L) to yield the free primary alcohol product of compound **481Cii**. A 15 mg (0.040 mmol) of the free alcohol of compound **481Cii** was reacted with 5-chloro-2-pyridinol (10 mg, 0.080 mmol), PPh<sub>3</sub> (21 mg, 0.080 mmol) and di-*tert*-butylazodicarboxylate (18 mg, 0.080 mmol) in THF (0.5 mL) in the manner described above and the resulting product was purified as described above to

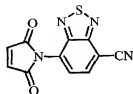
yield 8 mg (41%) of compound **481E** as a white solid. HPLC: 99% at 2.93 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H<sub>3</sub>PO<sub>4</sub>, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 486.2 [M+H]<sup>+</sup>.

### Example 482

[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-7-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482F) & [3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-7-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482G)



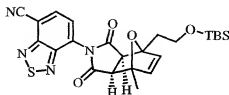
- A. 7-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-benzo[1,2,5]thiadiazole-4-carbonitrile (**482A**)



Maleic anhydride (667 mg, 6.80 mmol) was added to a solution of compound **424A** (600 mg, 3.41 mmol) in THF (9 mL). The mixture was heated at 110°C for 10 h. The reaction was concentrated under reduced pressure and acetic anhydride (1 mL) was added to the residue. The reaction mixture was heated at 75°C for 30 min and then cooled to rt. Purification by flash chromatography on silica gel eluting with 3% acetone/CHCl<sub>3</sub> gave 758 mg (2.96 mmol, 67%) of compound **482A**. HPLC: 97% at 1.98

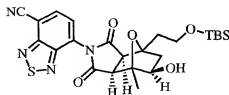
min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, monitoring at 220 nm). MS (ES): *m/z* 257.01 [M+H]<sup>+</sup>.

- B.** (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-7-[4-[2-[[**(1,1-Dimethylethyl)dimethylsilyl**]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (**482B**)



A solution of compound **482A** (758 mg, 2.96 mmol) and compound **204A** (711 mg, 2.96 mmol) in benzene (2 mL) and acetone (2 mL) was heated at 60°C for 6 h. The reaction mixture was concentrated *in vacuo* at 42°C for 40 min to give 1.5 g of crude compound **482B**, which was used directly in the next step without further purification.

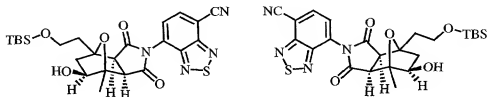
- C.** (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-7-[7-[2-[[**(1,1-Dimethylethyl)dimethylsilyl**]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (**482C**)



Borane-dimethylsulfide complex (0.66 mL, 6.96 mmol) was added to a solution of compound **482B** (1.15 g, 2.32 mmol) in THF (6 mL) at 0°C. After stirring at 0°C for 2 h, the reaction mixture was quenched with phosphate buffer (60 mL, pH 7.2) and then EtOH (35 mL), H<sub>2</sub>O<sub>2</sub> (8 mL, 30% aq.) and THF (4 mL) were added. The reaction mixture was stirred at 0°C for 1 h and was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 100 mL). The

combined organic layers were washed with 10% aq.  $\text{Na}_2\text{SO}_3$  (1 x 160 mL) followed by brine (1 x 160 mL) and dried over  $\text{Na}_2\text{SO}_4$ . Purification by flash chromatography on silica gel eluting with 10% acetone/ $\text{CHCl}_3$  gave 250 mg (0.486 mmol, 21%) of compound **482C** as an orange solid. HPLC: 85% at 3.70 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2%  $\text{H}_3\text{PO}_4$ , monitoring at 220 nm). MS (ES):  $m/z$  515.27  $[\text{M}+\text{H}]^+$ .

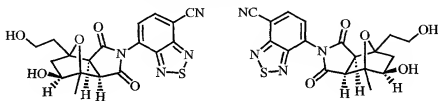
- D. [3a*R*-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-7-[7-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile & [3a*S*-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-7-[7-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (**482Di** & **482Dii**)



The racemic compounds **482C** was separated by normal phase preparative chiral HPLC using a Chiralcel OD column (5 cm x 50 cm), eluting with 10% EtOH in hexane at 50 mL/min to give the faster eluting compound **482Di** (Chiral HPLC: 11.89 min; CHIRALCEL OD 4.6 x 250 mm column; isocratic elution with 12% EtOH in hexane at 2 mL/min) and the slower eluting compound **482Dii** (Chiral HPLC: 16.10 min; CHIRALCEL OD 4.6 x 250 mm column; isocratic elution with 12% EtOH in hexane at 2 mL/min). The absolute conformation for compounds **482Di** & **482Dii** was not established. For simplicity in nomenclature, compound **482Di** is designated herein as having an “R” configuration and compound **482Dii** as having an “S” configuration. Enantiomerically pure products derived from compound **482Di** are designated herein as

having a "R" configuration and enantiomerically pure products derived from compound **482Dii** are designated herein as having an "S" configuration.

- E. [3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-7-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (**482Ei**) & [3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-7-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (**482Eii**)



Compound **482Di** (91 mg, 0.18 mmol) was dissolved in 2% 12 N HCl/EtOH (3.0 mL) and the mixture was stirred at rt for 20 min. Cold sat. NaHCO<sub>3</sub> was added to the mixture until it was basic (pH 8). The reaction was extracted with EtOAc. The organic layers were then washed with brine and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 73 mg (0.18 mmol, 100%) compound **482Ei** as a yellow solid which was not purified further. HPLC: 95% at 1.73 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, monitoring at 220 nm). MS (ES): *m/z* 401.13 [M+H]<sup>+</sup>.

Compound **482Dii** (90 mg, 0.17 mmol) was dissolved in 2% 12 N HCl/EtOH (3.0 mL) and the mixture was stirred at rt for 20 min. Cold sat. NaHCO<sub>3</sub> was added to the mixture until it was basic (pH 8). The reaction was extracted with EtOAc. The organic layers were then washed with brine and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 70 mg (0.17 mmol, 100%) compound **482Eii** as an orange solid which was not purified further. HPLC: 90% at 1.74 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, monitoring at 220 nm). MS (ES): *m/z* 401.14 [M+H]<sup>+</sup>.

**F. [3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-7-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482F)**

DBAD (21 mg, 0.090 mmol) was added to a solution of PPh<sub>3</sub> (24 mg, 0.090 mmol) in THF (0.4 mL). After stirring for 10 min, 5-chloro-2-pyridinol (12 mg, 0.090 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound **482Ei** (18 mg, 0.045 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was then concentrated under reduced pressure. Purification by preparative TLC eluting with 20% acetone/CHCl<sub>3</sub> gave 12 mg (0.023 mmol, 52%) of compound **482F**. HPLC: 98% at 3.15 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, monitoring at 220 nm). MS (ES): m/z 512.11 [M+H]<sup>+</sup>.

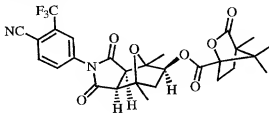
**G. [3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-7-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482G)**

DBAD (21 mg, 0.090 mmol) was added to a solution of PPh<sub>3</sub> (24 mg, 0.090 mmol) in THF (0.4 mL). After stirring for 10 min, 5-chloro-2-pyridinol (12 mg, 0.090 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound **482Eii** (18 mg, 0.045 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was then concentrated under reduced pressure. Purification by preparative TLC eluting with 20% acetone/CHCl<sub>3</sub> gave 11 mg (0.021 mmol, 47.0%) of compound **482G**. HPLC: 98% at 3.15 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H<sub>3</sub>PO<sub>4</sub>, monitoring at 220 nm). MS (ES): m/z 512.15 [M+H]<sup>+</sup>.



**Example 483**

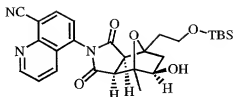
(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid, [3*aS*-(3*a* $\alpha$ ,4*\beta*,5*\beta*,7*\beta*,7*a* $\alpha$ )]-2-[4-cyano-3-(trifluoromethyl)phenyl]octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1*H*-isoindol-5-yl ester (483)



To a solution of compound **471Di** (25 mg, 0.066 mmol) in 0.25 mL of CH<sub>2</sub>Cl<sub>2</sub> at rt and under argon, was added a solution of (1*S*)-(-)-camphanic acid (20 mg, 0.10 mmol) in 0.2 mL of CH<sub>2</sub>Cl<sub>2</sub>. A solution of DCC (20 mg, 0.10 mmol) in 0.25 mL of CH<sub>2</sub>Cl<sub>2</sub> was then added followed by DMAP (4.0 mg, 0.034 mmol). A white precipitate was obtained immediately and stirring was continued overnight. The precipitate was removed by filtration and the filtrate was diluted with EtOAc. The resulting solution was washed with 1*N* HCl, brine, sat. NaHCO<sub>3</sub>, and brine then dried over MgSO<sub>4</sub>. Concentration *in vacuo* afforded a viscous oily residue. The crude material was subjected to flash chromatography on a 20 cm<sup>3</sup> column of silica gel eluting with 50% EtOAc in hexanes to 32 mg of a white solid. Recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexane yielded 20 mg (86%) of compound **483** as large crystals. This material was subjected to X-ray crystal diffraction studies to elucidate the exact stereochemistry of compound **471Di** as referenced to the known fixed stereochemistry of the (1*S*)-(-)-camphanic acid appendage. LCMS: 100% at 1.9 min (retention time) (Phenomenex Luna C18 column, 2 x 30 mm, 0-100% aqueous acetonitrile over 3 min containing 10 mM NH<sub>4</sub>OAc at 1 mL/min, monitoring at 220 nm). MS (ESI): *m/z* 559.3 [M-H].

**Example 484**

(3*a* $\alpha$ ,4*\beta*,5*\beta*,7*\beta*,7*a* $\alpha$ )-5-[7-[2-[(1,1-Dimethylethyl)dimethylsilyloxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-8-quinolinecarbonitrile (484)



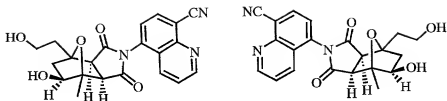
To a dry, 3-necked, 25 mL round-bottom was added  $\text{TiCl}_2\text{Cp}_2$  (0.500 g, 2.01 mmol) and THF (4 mL) to give a deep red solution. Activated zinc dust (0.392 g, 6 mmol, prepared as described in Fieser and Fieser, Volume 1, p. 1276) was added and the suspension was stirred for 30 min during which time the color changed from brick-red to emerald-green. The unreacted zinc dust was allowed to settle. In a separate 3-necked, 25 mL round-bottom flask was added compound **464F** (0.202 g, 0.399 mmol), THF (1 mL) and 1,4-cyclohexadiene (0.380 mL, 4.02 mmol). The Ti(III) reagent (0.90 mL, 0.45 mmol) was added via an addition funnel with a cotton plug at the bottom rinsing with THF (1 mL). After 1 h, HPLC showed ~ 50% conversion and an additional 0.9 mL (0.45 mmol) of the titanium reagent was added. After 1 h, HPLC showed complete consumption of starting material. Saturated ammonium chloride (5 mL) was added, followed by 10 mL of EtOAc. The organic layer was separated, washed with brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to give the crude product as an orange semi-solid. The crude material was purified by flash chromatography on silica gel eluting with 50%  $\text{CH}_2\text{Cl}_2$ /48% EtOAc/2% MeOH to give 0.10 g (59%) of compound **484** as a light yellow foam. HPLC: 91% at 3.65 min (retention time) (YMC S5 ODS column, 4.6x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  508.27  $[\text{M}+\text{H}]^+$ .

#### Example 485

[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[7-[2-[[[1,1-Dimethylethyl]dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (485i) & [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-

### Example 486

## 399



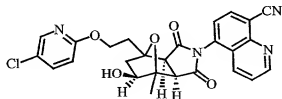
Compounds **485i** & **485ii** were converted to the free primary alcohol products as described in example **466** to give compounds **486i** and **486ii** as white solids.

Compound **486i**: HPLC: 98% at 1.650 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  394.21  $[M+H]^+$ .

Compound **486ii**: HPLC: 98% at 1.663 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  394.20  $[M+H]^+$ .

#### Example 487

[3a*R*-(3a*α*,4*β*,7*β*,7a*α*)]-5-[7-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-8-quinolinecarbonitrile  
(**487**)

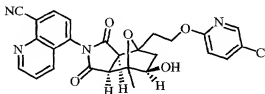


DBAD (0.088 g, 0.38 mmol) was added to a solution of triphenylphosphine (0.100 g, 0.382 mmol) in THF (1.0 mL) at 22°C and stirred for 10 min. 5-Chloro-2-pyridinol (0.049 g, 0.38 mmol) was added as a solid and stirring was continued for 10 min. The reaction mixture was added to compound **486i** (0.100 g, 0.250 mmol) in THF (1.0 mL). After stirring for 3 h, the reaction was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 20-50% acetone/chloroform to give 0.080 g (63%) of compound **487** as a white solid. HPLC: 100% at 3.023 min (retention time)

(YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  505.16  $[M+H]^+$ .

#### Example 488

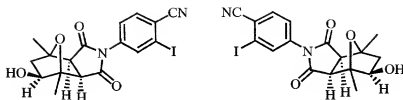
[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile  
(488)



DBAD (0.088 g, 0.38 mmol) was added to a solution of triphenylphosphine (0.100 g, 0.382 mol) in THF (1.0 mL) at 22°C and stirred for 10 min. 5-Chloro-2-pyridinol (0.049 g, 0.38 mmol) was added as a solid and stirring was continued for 10 min. The reaction mixture was added to compound **486ii** (0.100 g, 0.250 mmol) in THF (1.0 mL). After stirring for 3 h, the reaction was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 10-50% acetone/chloroform to give 0.080 g (63%) of compound **488** as a white solid. HPLC: 95% at 3.030 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  505.12  $[M+H]^+$ .

#### Example 489

[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489Gi) & [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489Gii)



**A. 2-Iodo-4-nitro-phenylamine (489A)**



To a mixture of iodine (46.0 g, 0.180 mol) and silver sulfate (56.3 g, 0.180 mol) in anhydrous ethanol (500 mL) was added 4-nitroaniline (25.0 g, 0.180 mol) and the reaction mixture was stirred for 5 h at rt. The resulting yellow solution was filtered and concentrated *in vacuo*. The resulting residue was dissolved into 400 mL ethyl acetate, washed with 1N sodium hydroxide solution (2 x 250 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 45.5 (95%) of compound **489A**, as a yellow solid. HPLC: 98% at 2.837 min (retention time) (Shimadzu VP-ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  265.08  $[M+H]^+$ .

**B. 2-Iodo-4-nitro-benzonitrile (489B)**



Compound **489A** (10.0 g, 37.9 mmol) was dissolved in a mixture of 20 mL 12 N HCl/40 mL water and then cooled to 0°C. To this mixture was slowly added a solution of sodium nitrite (5.23 g, 75.8 mmol) in 10 mL water while maintaining the reaction temperature at 0°C. The reaction was stirred for 1 h at 0°C and then slowly added to a

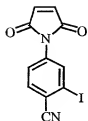
mechanically stirred solution of freshly prepared cuprous cyanide (3.0 g, 33 mmol, prepared as described in Vogel's Textbook of Practical Organic Chemistry, 5<sup>th</sup> edition, pg. 429) and potassium cyanide (6.30 g, 96.7 mmol) in water (50 mL) at 50°C. The reaction was stirred for 1 h at 50°C, cooled to 25°C and extracted with methylene chloride (2 x 200 mL). The organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography on silica gel eluting with 4:1 hexane:ethyl acetate to yield 4.6 g (44%) of compound **489B** as an orange solid. HPLC: 98% at 2.647 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**C. 4-Amino-2-iodo-benzonitrile (489C)**

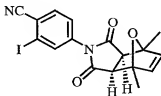


A mixture of compound **489B** (4.60 g, 16.8 mmol), tetrahydrofuran (75 mL), ethanol (100 mL), ammonium chloride solution (1.51 g, 28.3 mmol, dissolved in 100 mL of water), and iron (325 mesh, 4.21 g, 75.4 mmol) was mechanically stirred. The reaction mixture was heated to reflux for 3 h or until all starting material was consumed. The reaction mixture was cooled, filtered through Celite and concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (200 mL) and washed with 1N sodium hydroxide (2 x 150 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield 3.97 g (97%) of compound **489C** as a dark solid. HPLC: 95% at 1.877 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 245.13 [M+H]<sup>+</sup>.

**D. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-iodo-benzonitrile (489D)**



**E.** (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl)-2-iodobenzonitrile (489E)

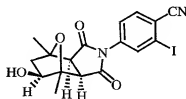


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methanol over 4 min containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 254 nm). MS (ES):  $m/z$  421.05[M+H]<sup>+</sup>.

**F. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489F)**



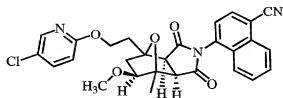
To a solution of compound **489E** (0.40 g, 0.95 mmol) in dry THF (5 mL) cooled to 0°C was added borane-dimethylsulfide complex (0.2 mL, 1.9 mmol, 10 M) and the reaction solution was allowed to warm to 25°C. After stirring for 30 min, the reaction was cooled to 0°C and pH 7 phosphate buffer (6.6 mL) was slowly added, followed by the addition of 30% hydrogen peroxide (0.7 mL). The reaction was stirred at 25°C for 1 h and then partitioned between ethyl acetate (100 mL) and water (100 mL). The organic portion was isolated, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel eluting with 3:1 methylene chloride:ethyl acetate to yield 0.11 g (25%) of compound **489F** as a white solid. HPLC: 99% at 2.527 min (retention time) (Shimadzu VP-ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  439.09 [M+H]<sup>+</sup>.

**G. [3a*R*-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489Gi) & [3a*S*-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489Gii)**

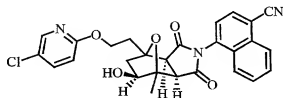
The racemic compounds **489F**, was separated into its individual antipodes by normal phase preparative chiral HPLC. A Chiralcel AD column (50 x 500 mm) was used with a flow rate of 50 mL/min (70% Isopropanol/hexanes) monitoring at 220 nm. The faster eluting antipode, compound **489Gi** had a retention time of 4.587 min and the slower eluting antipode, compound **489Gii** had a retention time of 6.496 min. Both antipodes were isolated as white solids after separation. The absolute conformation for compounds **489Gi** & **489Gii** was not established. For simplicity in nomenclature, compound **489Gi** is designated herein as having an "R" configuration and compound **489Gii** as having an "S" configuration.

### Example 490

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (490B)



A. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (490A)



A mixture of triphenylphosphine (166 mg, 0.633 mmol) and DBAD (146 mg, 0.633 mmol) was dissolved in THF (4 mL) under nitrogen and the yellow solution was stirred for 10 min. 5-Chloro-pyridin-2-ol (82 mg, 0.63 mmol) was added and the mixture was stirred for 5 min after which compound **242B** (165 mg, 0.327 mmol) was added. The mixture was stirred for 12 h and the solvent was removed under a stream of nitrogen.

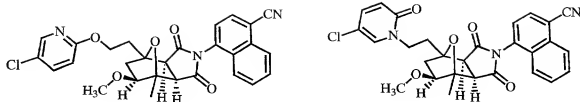
The resulting oil was adsorb onto silica gel (1 g) and purified by flash chromatography on a Jones Chromatography silica cartridge (5 g/25 mL) eluting with a gradient of 0-50% acetone in chloroform to give 79.4 mg (47%) of compound **490A** as a white foam. HPLC: 99% at 3.48 min (retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  504.17  $[M+H]^+$ .

**B. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (490B)**

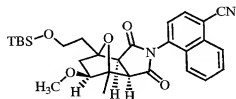
Compound **490A** (24 mg, 0.048 mmol) was dried into a 1 dram vial with a magnetic stir bar. Silver oxide (57 mg, 0.24 mmol),  $CH_3CN$  (500  $\mu$ L) and iodomethane (20  $\mu$ L, 0.32 mmol) were added under nitrogen and the mixture was put in a heated block (82°C) and stirred for 14 h. The mixture turned brown after 20 min then green. The mixture was filtered through Celite and Florisil and was purified by reverse phase preparative HPLC (Shimadzu Shimpac VP ODS column, 20 x 50 mm, 0-100% aqueous methanol over 6 min containing 0.1% TFA, monitoring at 220 nm) to give 6.9 mg (28%) of compound **490B** as a white foam. HPLC: 99% at 3.64 min, 3.76 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  518.19  $[M+H]^+$ .

**Example 491**

**[3 $\alpha$ R-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (491Ci) & [3 $\alpha$ R-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-(5-Chloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (491Cii)**

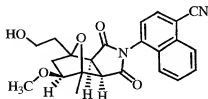


- A. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**491A**)



Compound **243Cii** (142 mg, 0.280 mmol) was dried into a 1 dram vial equipped with a magnetic stir-bar and a Teflon lined cap. Silver oxide (324 mg, 1.40 mmol), CH<sub>3</sub>CN (3 mL) and iodomethane (90  $\mu$ L, 1.4 mmol) were added under nitrogen and the mixture was put in a heated block (82°C). The reaction was stirred overnight, then filtered through Celite and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel eluting with a gradient of 0-50% acetone in chloroform to yield 62.2 mg (43%) of compound **491A**. HPLC: 99% at 3.87 & 3.95 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 521.37 [M+H]<sup>+</sup>.

- B. 3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-7-(2-hydroxyethyl)-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**491B**)



Compound **491A** (62.2 mg, 0.119 mmol) was dissolved in ethanol (2 mL) and 12 N hydrochloric acid (50  $\mu$ L) was added and the mixture was stirred for 10 min. The solvent was removed *in vacuo* and the product was purified by flash chromatography on silica gel eluting with a gradient of 0-20% acetone in chloroform to yield 40.3 mg (83%) of compound **491B** as a white solid. HPLC: 96% at 2.30 & 2.45 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  407.22  $[M+H]^+$ .

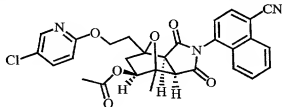
- C. **[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile, slow eluting enantiomer (491Ci) & [3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-(5-Chloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile (491Cii)**

Triphenylphosphine (40 mg, 0.15 mmol) and DBAD (35 mg, 0.15 mmol) were dissolved in THF under nitrogen and stirred 10 min. 5-Chloropyridin-2-ol (20 mg, 0.15 mmol) was added and the mixture was stirred for 5 min. Compound **491B** (40.3 mg, 0.0991 mmol) was added and the resulting mixture was stirred for 2.5 h. The solvent was concentrated *in vacuo* and the resulting residue was purified by chromatography over Florisil (1.3 g) eluting with a gradient of 0-40% acetone in chloroform to give 140 mg of a mixture of **491Ci**, **491Cii** and DBAD. The oil was suspended in dichloromethane (3 mL) and trifluoroacetic acid (2 mL) was added. After 45 min, the solvent was removed *in vacuo* and the resulting oil was partitioned between saturated sodium bicarbonate (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried over magnesium sulfate. Purification by reverse phase preparative HPLC (Shimadzu Shimpac VP ODS column, 20 x 50 mm, 0-100% aqueous methanol over 6 min containing 0.1% TFA, monitoring at 220 nm) gave 22 mg (44%) of compound **491Ci** and 4.6 mg (9% yield) of compound **491Cii**. Compound

**491Ci:** HPLC: 95% at 3.50 min (retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  518.28  $[M+H]^+$ . Compound **491Cii:** HPLC: 85% at 2.94 & 3.07 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  518.27  $[M+H]^+$ .

#### Example 492

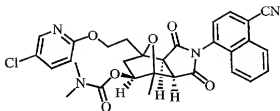
[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[5-(Acetvloxy)-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, slow eluting enantiomer (492)



Acetyl chloride (25  $\mu$ L, 0.35 mmol) was added to a solution of compound **490A** (30 mg, 0.060 mmol) in pyridine (600  $\mu$ L). The mixture was stirred overnight, diluted with hydrochloric acid (0.5 N, 10 mL), extracted with chloroform (3 x 7 mL). The organic layers were combined, washed with water (3 x 4 mL) and brine (4 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with a gradient of 0-50% acetone in chloroform gave 17 mg (53%) of compound **492**. HPLC: 99% at 3.48 & 3.63 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  546.15  $[M+H]^+$ .

#### Example 493

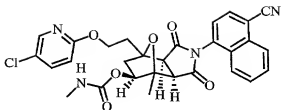
Dimethylcarbamic acid, [3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]-2-(4-cyano-1-naphthalenyl)octahydro-4-methyl-1,3-dioxo-4,7-epoxy-1H-isoindol-5-yl ester, slow eluting enantiomer (493)



To a solution of compound **490A** (30 mg, 0.060 mmol) in pyridine (300  $\mu$ L) was added dimethylcarbamyl chloride (28  $\mu$ L, 0.30 mmol) and the mixture was stirred at 25°C for 12 h. An additional portion of dimethylcarbamyl chloride (28  $\mu$ L, 0.30 mmol) was added and the reaction was heated at 70°C for 12 h. A third portion of dimethylcarbamoyl chloride (28  $\mu$ L, 0.30 mmol) as well as pyridine (300  $\mu$ L) were added and the mixture was stirred at 100°C for 24 h. The solution was diluted with 0.5 N HCl (10 mL) and extracted with chloroform (3 x 7 mL). The organic layers were combined and washed with water (3 x 4 mL) and brine (4 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (Shimadzu Shimpac VP ODS column, 20 x 50 mm, 0-100% aqueous methanol over 6 min containing 0.1% TFA, monitoring at 220 nm) gave 15.7 mg (46%) of compound **493** as a white solid. HPLC: 99% at 3.52 min & 3.69 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  575.10  $[M+H]^+$ .

#### **Example 494**

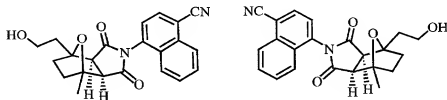
**[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-5-[[[(methylamino)carbonyl]oxy]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, slow eluting enantiomer (494)**



Methyl isocyanate (36  $\mu$ L, 0.60 mmol) was added to a solution of compound **490A** (30 mg, 0.060 mmol) in dioxane (600  $\mu$ L) and was heated at 80°C overnight. An additional portion of methyl isocyanate (36  $\mu$ L, 0.60 mmol) was added and the mixture was heated at 100°C for 24 h. A third portion of methyl isocyanate (36  $\mu$ L, 0.60 mmol) was added and the mixture was stirred at 100°C for 24 h. The solvent was removed *in vacuo* and the oil was purified by reverse phase preparative HPLC (Shimadzu Shimpac VP ODS column, 20 x 50 mm, 0-100% aqueous methanol over 6 min containing 0.1% TFA, monitoring at 220 nm) to give 20 mg (59%) of compound **494** as a clear glass. HPLC: 99% at 3.33 min & 3.42 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  561.08  $[M+H]^+$ .

#### Example 495

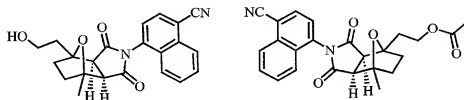
[3aR(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (495Ai) & [3aS(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (495B)



- A. [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (495Ai) &



(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[2-(Acetyloxy)ethyl]-2-(4-cyano-1-naphthalenyl)hexahydro-7-methyl-4,7-epoxy-1H-isindole-1,3(2H)-dione (495Aii)



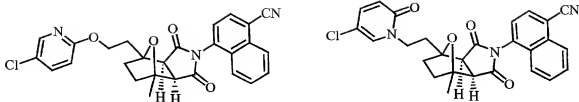
Racemic compound **223B** (10.26 g, 27.26 mmol) was dissolved in anhydrous THF (500 mL) in a 10 L bottle. *tert*-Butyl methyl ether (4.86 L), vinyl acetate (216 mL) and Lipase (108 g, [Sigma, Lipase type II, crude from Porcine pancreas, product No. L3126, Lot No. 021K1445]) were added. The reaction mixture was agitated for 24 h at rt and the reaction was monitored by HPLC using the following conditions: A 200  $\mu$ L sample of the reaction mixture was filtered, dried under a stream of nitrogen and subjected to HPLC analysis (YMC ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). The reaction was stopped after 60% of the starting material was consumed. The enzyme was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in  $\text{CHCl}_3$  and absorbed onto silica gel. Purification by flash chromatography on silica gel eluting with a gradient of 1-5% MeOH in  $\text{CHCl}_3$  gave 3.78 g (37%) of compound **495Ai** and 6.84 g (60%) of compound **495Aii**, both as white solids. Compound **495Ai**: HPLC: 99% at 3.47 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  377.09  $[\text{M}+\text{H}]^+$ . Normal phase preparative chiral HPLC: 37.8 min (retention time) (chiralpak AD column, 4.6 x 250 mm, 10 micron, 40°C, isocratic elution with 8% EtOH/MeOH (1:1) in heptane, monitoring at 220 nm), 99% ee. Compound **495Aii**: HPLC: 99% at 2.92 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm).

**B. [3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (495B)**

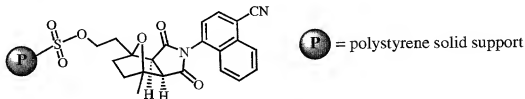
Lipase (134 g, [Sigma, Lipase type II, crude from Porcine pancreas, product No. L3126, Lot No. 021K1445]) was added to 3.5 L of deionized water. The mixture was centrifuged to remove most of the suspended material. The pH of the supernatant was adjusted to 7.06 with 1N sodium hydroxide and a solution of compound **495Aii** (8.04 g, 19.2 mmol) in TBME (1.5 L) was added. The pH was increased to 7.16 by addition of 1N sodium hydroxide. The reaction mixture was agitated at rt and was monitored by analytical HPLC as described in Example **495A**. After 30 min, the reaction was filtered through Celite and the filtrate was extracted with ethyl acetate (4 x 1 L) until HPLC showed that all the alcohol has been removed. The organic fractions were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (Jones, 50 g column) using a gradient of 0-70% acetone in chloroform followed by 5% MeOH in chloroform gave 2.44 g (33%) of compound **495B** as a white solid. HPLC: 99% at 2.89 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 377.09 [M+H]<sup>+</sup>. Normal phase preparative chiral HPLC: 11.1 min (retention time) (chiralpak AD column, 4.6 x 250 mm, 10 micron, 40°C, isocratic elution with 8% EtOH/MeOH (1:1) in heptane, monitoring at 220 nm), 95% ee.

**Example 496**

**[3aR-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (496Bi) & [3aR-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-(5-Chloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (496Bii)]**



#### A. Preparation of solid Support (496A)



A mixture of anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) and pyridine (10 mL) was added under nitrogen to chlorosulfonylpolystyrene (Argonaut, 1.70 mmol/g, 3.0 g, 5.1 mmol) and compound **495Ai** (3.78 g, 10.0 mmol) in a polymer synthesis tube. The mixture turned into a yellow gel and was vigorously shaken (wrist action shaker for 4 h.). All the solvents were absorbed by the resin and it looked dry. The resin was washed in portions with  $\text{CH}_2\text{Cl}_2$  (200 mL) and the washes were combined and extracted with 200 mL 1N HCl. The HCl fraction was re-extracted with ethyl acetate (200 mL). The organic fractions were combined and extracted with water (50 mL), brine (50 mL) and the organic fractions were dried over sodium sulfate, filtered and concentrated to give 2.1 g of resin bound compound **496A** (89% loaded based on recovered unbound compound **495Ai**). The resin was washed consecutively with DMF (5X), DMF : water (3:1, 5X), THF (3X) and  $\text{CH}_2\text{Cl}_2$  (3X) (~30 mL each wash). The resin was dried *in vacuo* for 1 h to yield 5.35 g of resin. The resin was still wet and was re-treated with the alcohol. The above described loading process was repeated using the recovered un-reacted compound **495Ai** from the above procedure. Recovered compound **495Ai** (2.1 g, 5.6 mmol) and anhydrous dichloromethane (15 mL) and pyridine (15 mL) and the resin were combined and subjected to the reaction conditions described above. The resulting resin was washed as described previously and dried *in vacuo* overnight to yield 4.49 g of resin (87% loaded based on recovered unbound compound **495Ai**). The starting alcohol was recovered from

the dichloromethane:pyridine mixture as described previously (2.04 g of white solid, which would suggest a 92% loading based on recovered alcohol). The resin weigh increase is usually more accurate for loading assessment. The resin loading was calculated to be 0.87 (determined by resin weight increase) X 1.08 mmol/g (calculated 100% loading) = 0.94 mmol/g. The resin was used as is for the next step.

**B. [3aR-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (496Bi) & [3aR-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-(5-Chloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (496Bii)**

The following procedure describes a general process by which arrays of compounds of Formula I can be made using automated approaches. Additional information on such automated synthetic approaches can be found in Example 8. Compounds **496Bi** & **496Bii** are an example of compounds made by such a procedure. For compounds **496Bi** & **496Bii**, 4-chloropyridinol represents the nucleophile reagent. A broader definition of the term nucleophile is contained in the body of this document and is well understood by one skilled in the art. A Bohdan MiniReactor equipped with a heating/cooling block was used with 0.5 Dram vials stacked over one another to achieve the same level as the reactor tubes. Resin (compound **496A**) was measured into the individual vials by using each Bohdan resin Transfer module plate "10 mg" and "20 mg" once. The weights of resin delivered ranged from 17-23 mg (0.016-0.022 mmol). Cesium carbonate was added using the Bohdan "20 mg" plate which delivered ~57-60 mg (0.17-0.18 mmol). The nucleophiles were weighted into 1 Dram vials and were diluted in THF to 0.06 M using a Tecan eight channel liquid handler. The resulting solutions (250  $\mu$ L, 0.015 mmol) were added manually via a micro-pipette to each of the reaction vials containing resin and the resulting array of reaction vials were placed in a Bohdan reactor. When the nucleophiles are amines, ~13  $\mu$ L of diisopropylethylamine was added to the THF solution of the

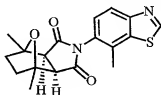
amine. The vials were capped (Teflon-lined) and the reactions were heated with orbital shaking (short stroke 500 rpm) at 70°C for 24 h. The reactions were cooled to 25°C and 1 mL of a mixture of heptane and ethyl acetate (1:1) was added followed by 0.5 mL of water. The organic layer was extracted manually and individually transferred to a synthesis block tube containing magnesium sulfate (~150 mg). The array of synthesis block tubes were simultaneously filtered and the filtrates were individually collected into microtubes (96 well block). The aqueous layer was re-extracted with 1 mL of a mixture of heptane and ethyl acetate (1:1), the organic layer was filtered as described above and the filtrate was individually collected as described above into the existing microtubes.

Analysis of the array of compounds prepared by the above procedure was performed using the following automated approach. A 120 µl portion of each of the above reaction (filtrates) was aliquoted into two 96 deep well blocks for analysis. The solvent was concentrated *in vacuo* and the plates were re-diluted with methanol (500 µL). One plate was analyzed by LCMS (Phenomenex ODS column, 4.6 x 50 mm, 4 mL/min, gradient 0% A to 100% B (A: 90% water, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% water, 0.1% TFA) and the other by flow-NMR (Varian Inova-500 MHz, MeOH, WET solvent suppression pulse sequence, 128 scans, 60 µl flow cell probe). The criteria for submission was: correct molecular ion present and HPLC/NMR purity >70%. Compounds which did not meet the desired criteria were purified by reverse phase preparative HPLC (Shimadzu UP-ODS column, 20 x 50 mm, 20 mL/min, gradient 40% B to 100% B in 6 min with 2 min hold (A: 90% water, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% water, 0.1% TFA). HPLC purification yielded 3.4 mg (21%) of compound **496Bi** as a glassy solid and 6.8 mg (41%) of compound **496Bii** as a glassy solid. Compound **496Bi**: HPLC: 96% at 3.47 min & 3.62 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, 4 mL/min, gradient 0% A to 100% B (A: 90% water, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% water, 0.1% TFA), monitoring at 220 nm). MS (ES):  $m/z$  487.94  $[M+H]^+$ . Compound **496Bii**: HPLC: 96% at 3.00 min & 3.12 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, 4 mL/min, gradient 0% A to 100% B (A: 90% water, 10% MeOH, 0.1% TFA;

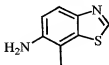
B: A: 90% MeOH, 10% water, 0.1% TFA), monitoring at 220 nm). MS (ES):  $m/z$  488.12  $[M+H]^+$ . Additional compounds made by this procedure are set forth in Table 17.

#### Example 497

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-(7-methyl-6-benzothiazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (497B)



#### A. 6-Amino-7-methylbenzothiazole (497A)



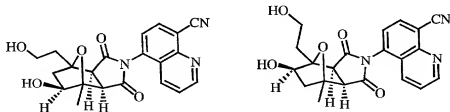
7-Methyl-6-nitrosobenzothiazole was prepared from 6-nitrobenzothiazole according to the general procedure described by Bartoli *et al. Synlett* 270 (1976). To a solution of 7-methyl-6-nitrosobenzothiazole (889 mg, 5.00 mmol) in AcOH (40 mL) at 70°C was added iron powder (325 mesh, 559 mg, 10.0 mmol) in a single portion. The resulting dark reaction mixture was stirred for 15 min before it was cooled and concentrated *in vacuo* to leave a residue which was partitioned between 1N HCl (50 mL) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The layers were separated and the organic layer was washed once with 1N HCl (25 mL). The combined aqueous layers were made basic by the addition of solid NaHCO<sub>3</sub> and were extracted twice with EtOAc. The organic phases were combined, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give 534 mg (65%) of compound **497A** as a light brown solid. HPLC: 96% at 0.55 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H<sub>3</sub>PO<sub>4</sub>, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  165.0  $[M+H]^+$ .

**B. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-(7-methyl-6-benzothiazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (497B)**

6-Amino-7-methylbenzothiazole (29 mg, 0.18 mmol), MgSO<sub>4</sub> (54 mg, 0.45 mmol), triethylamine (125  $\mu$ L, 0.897 mmol) and compound **20A** (52 mg, 0.26 mmol) were taken up in 0.18 mL of DME and placed in a sealed tube. The sealed tube was heated at 135°C for 14 h. The cooled reaction mixture was filtered through a short pad of Celite eluting with EtOAc and the solvent was removed *in vacuo*. The residue was purified by reverse phase preparative HPLC (YMC S5 ODS column, 20 x 100 mm, eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min, monitoring at 220 nm). Concentration of the desired fractions afforded a residue which was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and sat. NaHCO<sub>3</sub> solution (10 mL). The aqueous layer was extracted once with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give 42 mg (68%) of compound **497B** as a tan solid. HPLC: 2.36 min & 2.55 min (atropisomers, retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 343.3 [M+H]<sup>+</sup>.

**Example 498**

**(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-5-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (498i) & (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-5-[Octahydro-5-hydroxy-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (498ii)**



Compound **464E** (0.500 g, 1.02 mmol) was dissolved in THF (5.00 mL) and cooled to 0°C. BH<sub>3</sub>•DMS (0.193 mL, 2.04 mmol) was then added slowly followed by warming to 25°C. After 1 h, the reaction was cooled to 0°C and pH 7 phosphate buffer (15.0 mL) was added resulting in the evolution of gas. EtOH (7.0 mL) and hydrogen peroxide (30%, 1.5 mL) were then added and the reaction was warmed to 25°C over 2 h. After 3 h, the mixture was extracted with methylene chloride (3 x 50 mL). The combined organic layers were washed once with brine and dried over anhydrous sodium sulfate. The product was complexed to boron after workup. All attempts to break up this complex failed to give the free product. The crude material was taken on to the next step without further purification.

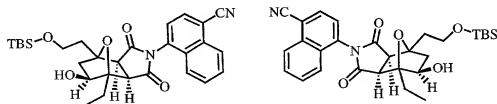
The crude reaction mixture was dissolved in 2% conc. HCl/MeOH (5.0 mL) at rt. After 1 h, the volatiles were removed *in vacuo* and the resulting residue was dissolved in methylene chloride and washed once with sat. aq. sodium bicarbonate and dried over anhydrous sodium sulfate. Solvent removal *in vacuo* gave the crude mixture of compounds **498i** and **498ii** as a yellow solid. The mixture of compounds was separated by reverse phase preparative HPLC: Compound **498i**: 17.994 min (retention time) & compound **498ii**: 19.767 min (retention time) (YMC S5 ODS column, 30 x 250 mm, 25 mL/min, 10-90% aqueous methanol over 35 min containing 0.1% TFA, monitoring at 220 nm). Solvent removal *in vacuo* gave 0.012 g (3%) of compound **498i** as a white solid and 0.009 g (2%) of compound **498ii** as a white solid. Compound **498i**: HPLC: 85% at 1.843 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 394.21 [M+H]<sup>+</sup>. Compound **498ii**: HPLC: 98% at 1.650 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 394.21 [M+H]<sup>+</sup>.

#### Example 499

[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[7-[2-[[[1,1-Dimethylethyl]dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-



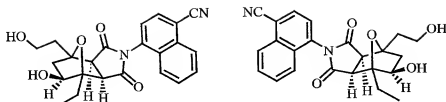
**naphthalenecarbonitrile (499i) & [3a*S*-(3α,4β,5β,7β,7α)]-4-[7-[2-[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (499ii)**



The racemic compound **434C** was separated into its individual antipodes by normal phase preparative chiral HPLC using a Chiracel AD column (5 cm x 50 cm), eluting with 8% EtOH in hexane at 50 mL/min to give the faster eluting compound **499i** (Chiral HPLC: 6.74 min; CHIRALCEL AD 4.6 x 250 mm column; isocratic elution with 10% EtOH in hexane at 2 mL/min) and the slower eluting compound **499ii** (Chiral HPLC: 9.99 min; CHIRALCEL AD 4.6 x 250 mm column; isocratic elution with 10% EtOH in hexane at 2 mL/min). For either compound **499i** or **499ii**: HPLC: 100% at 3.96 min (retention time) (YMC CombiSreen ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  521.25  $[M+H]^+$ . The absolute stereochemistry for compounds **499i** & **499ii** was not established. For simplicity in nomenclature, compound **499i** is designated herein as having an "R" configuration and compound **499ii** as having an "S" configuration. Enantiomerically pure products derived from compound **499i** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **499ii** are designated herein as having an "S" configuration.

**Example 500**

**[3a*R*-(3α,4β,5β,7β,7α)]-4-[4-Ethyloctahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (500i) & [3a*S*-(3α,4β,5β,7β,7α)]-4-[4-Ethyloctahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (500ii)**

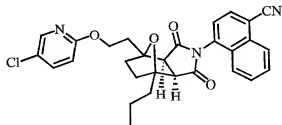


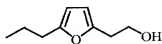
Compound **499i** (24.0 mg, 0.0461 mmol) was dissolved in 2% conc. HCl/EtOH (0.8 mL) and the mixture was stirred at rt for 20 min. Cold sat.  $\text{NaHCO}_3$  was added to the mixture until the solution reached pH 8, then extracted with EtOAc. The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 14.7 mg (78%) of compound **500i** as a white solid which did not require further purification. HPLC: 95% at 2.40 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2%  $\text{H}_3\text{PO}_4$ , monitoring at 220 nm).

Compound **499ii** (18.0 mg, 0.0346 mmol) was dissolved in 2% conc. HCl/EtOH (0.6 mL) and the mixture was stirred at rt for 20 min. Cold sat.  $\text{NaHCO}_3$  was added to the mixture until the solution reached pH 8, then extracted with EtOAc. The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 14.1 mg (99%) of compound **500ii** as a white solid which did not require further purification. HPLC: 95% at 2.40 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2%  $\text{H}_3\text{PO}_4$ , monitoring at 220 nm).

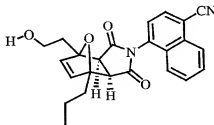
#### Example 501

[3aR-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (501D)



**A. 2-(5-Propyl-furan-2-yl)-ethanol (501A)**

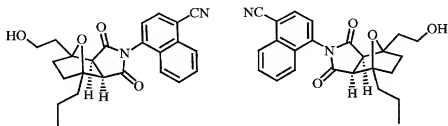
To a solution of 2-propylfuran (3.00 g, 31.2 mmol) in THF (31 mL) at  $-78^{\circ}\text{C}$  was added *n*-BuLi (15.0 mL, 2.5 M, 37.4 mmol) dropwise over 10 min. The reaction was warmed to rt and stirred for 3.5 h. After cooling to  $0^{\circ}\text{C}$ , ethylene oxide (2.33 mL, 46.8 mmol) was added, the reaction was warmed to rt and stirring was continued for 19 h. The reaction was then cooled to  $0^{\circ}\text{C}$  and quenched with sat.  $\text{NH}_4\text{Cl}$  (20 mL), followed by extraction with  $\text{Et}_2\text{O}$  (2 x 50 mL). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give 4.38 g (91%) of compound **501A** as a bright orange oil. This material was used without further purification. HPLC: 94% at 2.91 min (retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  137.13  $[\text{M}-\text{H}_2\text{O}+\text{H}]^+$ .

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[1,3,3a,4,7,7a-Hexahydro-4-(2-hydroxyethyl)-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (501B)**

A suspension of 2-(5-propyl-furan-2-yl)-ethanol (2.50 g, 16.2 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (4.02 g, 16.2 mmol) in benzene (16 mL) was warmed to  $60^{\circ}\text{C}$ . After 3 h, the reaction was concentrated *in vacuo* to give a brown foam. Methanol (17 mL) was added and the mixture was sonicated to give a fine beige solid with a brown supernatant. Filtration gave 1.75 g (27%) of compound **501B** as

an off-white solid. This material was used without further purification. HPLC: 85% at 3.02 min & 3.14 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  403.31  $[M+H]^+$ .

**C. [3a*R*-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-(2-hydroxyethyl)-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (501Ci) & [3a*S*-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-(2-hydroxyethyl)-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (501Cii)**



To a suspension of compound **501B** (1.60 g, 3.97 mmol) in ethyl acetate (79.5 mL) was added 10% Pd/C (0.422 g, 0.397 mmol). Hydrogen gas was bubbled through the reaction for several minutes and the reaction was allowed to stir under a hydrogen atmosphere for 3 h. The reaction was filtered through Celite and the filtrate was concentrated *in vacuo* to give a white solid (1.74 g). The crude material was dissolved in minimum amount of methylene chloride and loaded on a 120 g silica gel ISCO cartridge. Elution with a step gradient of 0 to 100% ethyl acetate/hexane gave 1.06 g (66%) of the racemic mixture of compounds **501Ci** & **501Cii** as a white foam. A 500 mg portion of the racemic mixture was separated by normal phase preparative chiral HPLC (Chiralpak AD; 5 x 50 cm column; isocratic elution with 13% MeOH/EtOH (1:1) in heptane at 50 mL/min, monitoring at 220 nm) to give 245 mg of the faster eluting enantiomer, compound **501Ci** and 245 mg of the slower eluting enantiomer, compound **501Cii**, both

as a white foams. Compound **501Ci**: Normal phase preparative chiral HPLC: 28.0 min (retention time), >95% ee (Chiralpak AD 4.6 x 250 mm column, eluting with 12% MeOH/EtOH (1:1) in heptane at 1.0 mL/min). HPLC: 99% at 3.04 & 3.17 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). HRMS  $m/z$  Calc'd for  $C_{24}H_{23}N_2O_4$  [M-H]<sup>-</sup>: 403.1658. Found 403.1644. Compound **501Cii**: Chiral HPLC: 65.7 min (retention time), >95% ee (Chiral HPLC: 65.7 min; >95% ee; Chiralpak AD 4.6 x 250 mm column; eluting with 12% MeOH/EtOH (1:1) in heptane at 1.0 mL/min). HPLC: 98% at 3.02 & 3.15 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4mL/min, monitoring at 220 nm). The absolute stereochemistry for compounds **501Ci** & **501Cii** was not established. For simplicity in nomenclature, compound **501Ci** is designated herein as having an "R" configuration and compound **501Cii** as having an "S" configuration. Enantiomerically pure products derived from compound **501Ci** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **501Cii** are designated herein as having an "S" configuration.

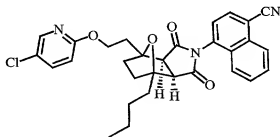
**D. [3aR-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (501D)**

To a solution of DBAD (17.1 mg, 0.0741 mmol) in THF (0.5 mL) was added PPh<sub>3</sub> (19.4 mg, 0.0741 mmol). After 10 min, 5-chloro-2-pyridinol (9.6 mg, 0.074 mmol) was added. After 5 min, compound **501Ci** (20.0 mg, 0.0494 mmol) was added. After 1 h, DBAD (17.1 mg, 0.0741 mmol), PPh<sub>3</sub> (19.4 mg, 0.0741 mmol), and 5-chloro-2-pyridinol (9.6 mg, 0.074 mmol) were added. After 3 h, the solvent was removed *in vacuo* to give a yellow residue. Preparative reverse phase HPLC (YMC ODS column, 20 x 100 mm, eluting with 40-100% aqueous methanol containing 0.1% TFA over 30 min, 25 mL/min, monitoring 220 nm) gave 9.5 mg (37%) of the trifluoroacetic acid salt of

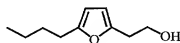
compound **501D** as a clear, colorless residue. HPLC: 99% at 7.88 min & 8.11 min (atropisomers, retention time) (Zorbax SB C18 4.6 x 75 mm, eluting with 10-90% aqueous methanol over containing 0.2% phosphoric acid over 8 min, 2.5 mL/min, monitoring at 220 nm). HRMS  $m/z$  Calc'd for  $C_{29}H_{27}N_3O_4Cl$   $[M+H]^+$ : 516.1690. Found 516.1676.

### Example 502

[3aR-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-Butyl-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (502D)



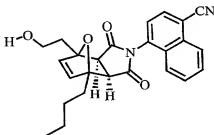
#### A. 2-(5-Butyl-furan-2-yl)-ethanol (502A)



To a solution of 2-butylfuran (3.00 g, 24.2 mmol) in THF (24 mL) at  $-78^{\circ}\text{C}$  was added *n*-BuLi (11.6 mL, 2.5 M, 29.0 mmol) dropwise over 10 min. The reaction was warmed to rt and stirred for 3.5 h. After cooling to  $0^{\circ}\text{C}$ , ethylene oxide (1.81 mL, 36.2 mmol) was added, the reaction was warmed to rt and stirring was continued for 19 h. The reaction was then cooled to  $0^{\circ}\text{C}$  and quenched with sat.  $\text{NH}_4\text{Cl}$  (20 mL), followed by extraction with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give 4.07 g (100%) compound **502A** as a bright orange oil. This material was used without further purification. HPLC: 96% at 3.23 min (retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2%

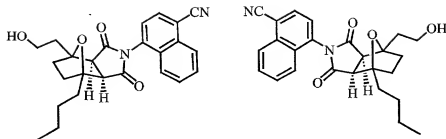
phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  169.22  $[M+H]^+$ .

- B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-Butyl-1,3,3a,4,7,7a-hexahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (502B)



A suspension of compound **502A** (2.50 g, 14.9 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (3.70 g, 14.9 mmol) in benzene (15 mL) was warmed to 60°C. After 3 h, the reaction was concentrated *in vacuo* to give a brown foam. Methanol (17 mL) was added and the mixture was sonicated to give a fine beige solid with an orange-brown supernatant. Filtration of the precipitate gave 2.64 g (44%) of compound **502B** as an off-white solid. This material was used without further purification. HPLC: 95% at 3.25 min & 3.35 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  417.29  $[M+H]^+$ .

- C. [3aR-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-Butyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (502Ci) & [3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-Butyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (502Cii)



To a suspension of compound **502C** (1.47 g, 3.52 mmol) in ethyl acetate (70 mL) was added 10% Pd/C (0.375 g, 0.352 mmol). Hydrogen was bubbled through the reaction for several minutes and the reaction was allowed to stir under a hydrogen atmosphere for 3 h. The reaction was filtered through Celite®, rinsing with ethyl acetate (2 x 70 mL). The filtrate was concentrated *in vacuo* to give a white foam (1.50 g). The crude material was dissolved in a minimum amount of methylene chloride and loaded on a 120 g silica gel ISCO cartridge. Elution with a step gradient of 0 to 100% ethyl acetate/hexane gave 1.05 g (74%) a racemic mixture of compounds **502Ci** & **502Cii** as a white foam. A 438 mg portion of racemic mixture of compounds **502Ci** & **502ii** was separated by normal phase preparative chiral HPLC (Chiralpak AD column, 5 x 50 cm, isocratic elution with 12% MeOH/EtOH (1:1) in heptane at 50 mL/min, monitoring at 220 nm) to yield 178 mg of the faster eluting enantiomer, compound **502Ci** as a white foam and 132 mg of the slower eluting enantiomer, compound **502Cii**, as a clear, viscous oil. Compound **502Ci**: Chiral HPLC: 25.5 min (retention time), >95% ee (Chiral HPLC: Chiralpak AD 4.6 x 250 mm column, eluting with 12% MeOH/EtOH (1:1) in heptane at 1.0 mL/min) and HPLC: 99% at 6.50 min & 6.71 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm) HRMS *m/z* Calc'd for  $C_{25}H_{25}N_2O_4$   $[M-H]^-$ : 417.1814. Found 417.1800. Compound **502Cii**: HPLC: 55.6 min (retention time), >95% ee (Chiral HPLC: Chiralpak AD 4.6 x 250 mm column; eluting with 12% MeOH/EtOH (1:1) in heptane at 1.0 mL/min). HPLC: 99% at 3.26 min & 3.38 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). The absolute



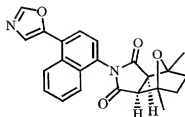
stereochemistry for compounds **502Ci** & **502Cii** was not established. For simplicity in nomenclature, compound **502Ci** is designated herein as having an "R" configuration and compound **502Cii** as having an "S" configuration. Enantiomerically pure products derived from compound **502Ci** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **502Cii** are designated herein as having an "S" configuration.

**D. [3a*R*-(3a*α*,4*β*,7*β*,7a*α*)]-4-[4-Butyl-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**502D**)**

To a solution of compound **502Ci** (20.0 mg, 0.0478 mmol), PPh<sub>3</sub> (37.6 mg, 0.143 mmol) and 5-chloro-2-pyridinol (18.6 mg, 0.143 mmol) in THF (0.5 mL) was added DBAD (33.0 mg, 0.143 mmol). The resulting solution was stirred at rt for 15.5 h. The solvent was removed *in vacuo* to give a yellow residue. Preparative HPLC (Shimadzu VP ODS column, 20 x 250 mm, eluting with 40-100% aqueous methanol containing 0.1% TFA over 30 min and 100% for 25 min, 25 mL/min, monitoring at 220 nm) gave 9.4 mg (37%) of the trifluoroacetic acid salt of compound **502D** as a clear, colorless residue. HPLC: 99% at 8.14 min & 8.36 min (atropisomers, retention time) (Zorbax SB C18 column, 4.6 x 75 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 8 min, 2.5 mL/min, monitoring at 220 nm). HRMS *m/z* Calc'd for C<sub>30</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>Cl [M+H]<sup>+</sup>: 530.1847. Found 530.1855.

**Example 503**

**(3a*α*,4*β*,7*β*,7a*α*)-Hexahydro-4,7-dimethyl-2-[4-(5-oxazolyl)-1-naphthalenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (**503E**)**



**A. (4-Cyano-naphthalen-1-yl)-carbamic acid tert-butyl ester (503A)**



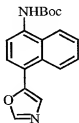
To a solution of 4-amino-1-naphthalenecarbonitrile (9.67 g, 57.5 mmol) in THF (100 mL) at rt was added, over 10 min, sodium hexamethyldisilazane (1.0 M in THF, 133 mL, 133 mmol). After stirring for 15 min, a solution of di-*t*-butyldicarbonate (15.1 g, 69.0 mmol) in THF (20 mL) was added. After stirring for 18 h at rt, the reaction mixture was partitioned between Et<sub>2</sub>O (400 mL) and saturated potassium bisulfate solution (200 mL). The organic layer was washed with saturated potassium bisulfate solution (200 mL), saturated sodium bicarbonate solution (200 mL) and brine (100 mL). Drying over anhydrous magnesium sulfate, treatment with decolorizing carbon and concentration *in vacuo*, afforded a residue that was partially purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane. The partially purified material was crystallized from ethyl acetate/hexane to give 5.26 g of compound **503A** as a colorless crystals. The mother liquor was concentrated and crystallized from ethyl acetate/hexane to give an additional 2.8 g of compound **503A** to yield a total of 8.06 g (52%) of compound **503A**. <sup>1</sup>HNMR (400 MHz, DMSO-*d*<sup>6</sup>): δ 9.81(s, 1H), 8.36 (d, 1H, *J* = 8.5 Hz), 8.11(m, 2H), 7.92 (d, 1H, *J* = 8 Hz), 7.78 (m, 1H), 7.67 (m, 1H), 1.53 (s, 9H).

**B. (4-Formyl-naphthalen-1-yl)-carbamic acid tert-butyl ester (503B)**



A mixture of compound **503A** (4.02 g, 15.0 mmol), Raney nickel (1.5 g), sodium hypophosphite (9.00 g, 86.5 mmol), pyridine (50 mL), water (25 mL) and acetic acid (25 mL) was stirred at 45°C for 5 h. The mixture was filtered through celite and the filter cake was rinsed with warm ethanol (100 mL). After adding water (600 mL) to the filtrate and allowing it to stand for 1 h, the resulting precipitate was filtered and rinsed with water. Drying *in vacuo* afforded 3.38 g of a white solid which was a 3:1 mixture of compounds **503B** & **503A**. The material was used in the next step without further purification. <sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.28 (s, 1H), 9.77 (s, 1H), 9.27 (d, 1H, *J* = 8.5 Hz), 8.31 (m, 1H), 8.13 (m, 1H), 8.00 (d, 1H, *J* = 8 Hz), 7.80 (m, 1H), 7.70 (m, 1H), 1.54 (s, 9H).

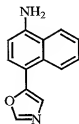
**C. (4-Oxazol-5-yl-naphthalen-1-yl)-carbamic acid *tert*-butyl ester (503C)**



The above mixture of compounds **503A** & **503B** (3.37 g, 10.0 mmol; corrected for presence of compound **503A**), toluene-sulfonylisocyanide (2.15 g, 11.0 mmol) and potassium carbonate (1.66 g, 12.0 mmol) in 50 mL of methanol was refluxed for 4 h. The reaction mixture was partitioned between water (200 mL) and chloroform (200 mL). After extracting the aqueous layer with chloroform (100 mL), the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel eluting with a gradient of 10-40%

ethyl acetate in hexane to give 1.35 g (44%) of compound **503C** as a white solid.  $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.45 (s, 1H), 8.57 (s, 1H), 8.20 (m, 2H), 7.76 (m, 2H), 7.64 (s, 1H), 7.62 (m, 2H), 1.51 (s, 9H).

**D. 4-Oxazol-5-yl-naphthalen-1-ylamine (503D)**



Compound **503C** (1.34 g, 4.3 mmol) was dissolved in trifluoroacetic acid (10 mL) and the resulting mixture was allowed to stand for 1 h at room temperature. After removing the volatiles *in vacuo*, the residue was co-evaporated from ethyl acetate/heptane (2 x 50 mL) to remove traces of trifluoroacetic acid. After partitioning the residue between ethyl acetate (100 mL) and 1N NaOH (75 mL), the organic layer was washed with brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford 900 mg (99%) of compound **503D** as a yellow crystalline solid. HPLC conditions: 95% at 0.92 min (retention time) (Phenomenex 5 micron ODS column, 4.6 x 30 mm, 10%-90% aqueous methanol over 2 min gradient with 0.1% TFA, monitoring at 254 nm.). MS (ES):  $m/z$  211.22  $[\text{M}+\text{H}]^+$ .

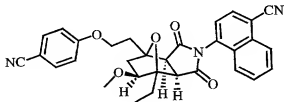
**E. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-Hexahydro-4,7-dimethyl-2-[4-(5-oxazolyl)-1-naphthalenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (503E)**

A mixture of compound **503D** (42 mg, 0.020 mmol) and **20A** (78 mg, 0.40 mmol) in acetic acid (1.0 mL) was refluxed for 18 h. The reaction mixture was cooled to rt, concentrated *in vacuo* and the residue was partitioned between ethyl acetate (30 mL) and saturated sodium bicarbonate solution (30 mL). The organic layer was isolated, dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography

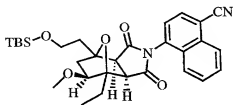
on a 2.5 x 15 cm silica gel column, using a gradient of 40-60% ethyl acetate in hexane gave 28 mg (37%) of compound **503E** as a white powder. HPLC: 99% at 1.46 min & 1.36 min (atropisomers, retention time) (Phenomenex 5 micron ODS 4.6 x 30 mm, 10%-90% aqueous methanol over 2 min gradient with 0.1% TFA, monitoring at 254 nm.). MS (ES):  $m/z$  389.10  $[M+H]^+$ .

### Example 504

**[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**504C**)**



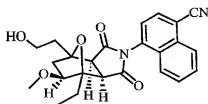
- A. **[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-[[1-(Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (**504A**)**



To a solution of compound **499ii** (0.235 g, 0.451 mmol) in  $CH_3CN$  (6 mL) was added silver oxide (0.523 g, 2.26 mmol) and iodomethane (0.56 mL, 9.0 mmol, stirred over  $K_2CO_3$  before addition). The resulting suspension was placed in a preheated oil bath (80°C). After 24 h, the reaction was cooled to rt, diluted with  $CH_3CN$  (20 mL), filtered through a plug of Celite, and concentrated *in vacuo* to give a brown gum. Purification by

flash chromatography on silica gel eluting with 30% ethyl acetate/hexanes gave 0.156 g (65%) of compound **504A** as a white solid. HPLC: 95% at 4.17 min & 4.25 min (atropisomers, retention time) (YMC CombiSreen ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  521.25  $[M+H]^+$ .

**B. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-Ethyl octahydro-7-(2-hydroxyethyl)-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (504B)**



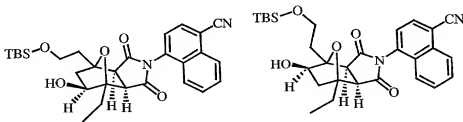
To a solution of compound **504A** (0.156 g, 0.292 mmol) in ethanol (6 mL) was added 1N HCl (0.44 mL, 0.44 mmol). After 20 min, the reaction was cooled to 0°C and quenched with sat. aq. NaHCO<sub>3</sub> (2 mL) to give a white suspension. Added H<sub>2</sub>O until the solid dissolved. The mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a white solid. Purification by flash chromatography on silica gel eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> gave 120 mg (99%) of compound **504A** as a white solid. HPLC: 98% at 5.17 and 5.44 min (atropisomers, retention time) (YMC CombiSreen ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 8 min, 2.5 mL/min, monitoring at 220 nm). HRMS  $m/z$  Calc'd for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>  $[M - H]^+$ : 419.1607. Found 419.1611.

**C. [3 $\alpha$ S-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyl octahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (504C)**

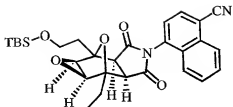
To a solution of compound **504B** (20 mg, 0.048 mmol) in anhydrous THF (0.5 mL) was added  $\text{PPh}_3$  (37.0 mg, 0.143 mmol), *para*-cyanophenol (17.0 mg, 0.143 mmol) and DBAD (32.0 mg, 0.143 mmol). After 30 min, the solution was concentrated to give a brown gum. Purification by reverse phase preparative HPLC (YMC S5 ODS column, 20 x 250 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 35 min, 20 mL/min, monitoring at 220 nm) gave 16 mg (64%) of compound **504C** as a clear, colorless oil. HPLC 98% at 6.84 and 7.10 min (atropisomers, retention time) (Zorbax SB C18 column, 4.6 x 75 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 8 min, 2.5 mL/min, monitoring at 220 nm). HRMS  $m/z$  Calc'd for  $\text{C}_{31}\text{H}_{27}\text{N}_3\text{O}_5$   $[\text{M} + \text{NH}_4]^+$ : 539.2295. Found 539.2302.

#### Example 505

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-4-[7-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (505Bi) & (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha\alpha$ )-4-[4-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-7-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (505Bii)



- A. (1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,7 $\alpha\alpha$ )-4-[2-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-6-ethyloctahydro-3,5-dioxo-2,6-epoxy-4H-oxireno[*f*]isoindol-4-yl]-1-naphthalenecarbonitrile (505A)



To a solution of compound **434B** (1.01 g, 2.01 mmol) in methylene chloride (20 mL) was added 60% *m*-CPBA (0.863 g, 3.00 mmol). After 48 h, the reaction was diluted with methylene chloride (50 mL) and washed with sat. Na<sub>2</sub>SO<sub>3</sub> (20 mL) and sat. NaHCO<sub>3</sub> (20 mL). The combined aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 1.01 g (97%) of compound **505A** as a yellow solid. This material used without further purification. HPLC: 95% at 4.22 min (retention time) (Phenomenex Luna C18 column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). HRMS *m/z* Calc'd for C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>Si [M-H]<sup>+</sup>: 517.2159. Found 517.2163.

**B. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]- 1-naphthalenecarbonitrile (**505Bi**) & (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-7-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]- 1-naphthalenecarbonitrile (**505Bii**)**

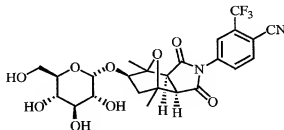
To a red solution of titanocene dichloride (0.500 g, 2.00 mmol) in anhydrous THF (4.0 mL) was added zinc dust (0.392 g, 6.00 mmol). The resulting suspension was vigorously stirred for 1 h under an argon atmosphere to give a green suspension. Excess zinc was removed by filtration through a 0.45  $\mu$ m microfilter to give a green solution of dicyclopentadienyl titanium (III) chloride. To a solution of compound **505A** (0.207 g, 0.399 mmol) and 1,4-cyclohexadiene (0.380 mL, 4.02 mmol) in anhydrous THF (1 mL)



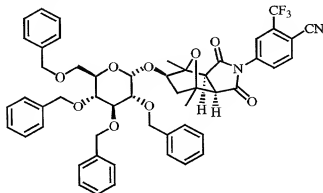
was added dropwise a 0.5 M solution of the above described dicyclopentadienyl titanium (III) chloride (0.9 mL, 0.45 mmol). After 1 h, an additional aliquot of the 0.5 M solution of dicyclopentadienyl titanium (III) chloride (0.9 mL, 0.45 mmol) was added and stirring was continued for 1 h. The reaction was then quenched with water (2 mL) and diluted with ethyl acetate (10 mL). The layers were separated and the organic layer was washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a yellow gum. The crude material was dissolved in a minimum amount of methylene chloride and loaded on a 35 g silica gel ISCO column. Gradient elution with 0-80% ethyl acetate in hexane gave 0.043 g (21%) of compound **505Bi** as a white solid and 0.023 g (11%) of compound **505Bii** as a white solid. Compound **505Bi**: HPLC: 3.92 min (retention time) (YMC CombiScreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 521.36 [M+H]<sup>+</sup>. Compound **505Bii**: HPLC: 91% at 3.97 min (retention time) (YMC CombiScreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): *m/z* 521.34 [M+H]<sup>+</sup>.

#### Example 506

**4-[[3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-5-( $\alpha$ -D-Glucopyranosyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (506B)**



- A. [3a*S*-(3α,4β,5β,7β,7α)]-4-[Octahydro-4,7-dimethyl-1,3-dioxo-5-[[2,3,4,6-tetrakis-*O*-(phenylmethyl)-α-D-glucopyranosyl]oxy]-4,7-epoxy-2*H*-isindol-2-yl]-2-(trifluoromethyl)benzonitrile (**506A**)



2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide was made according to the procedure by Spohr *et al. Can. J. Chem.* **71**, 1928-42 (1993). Oxalyl bromide (0.48 mL, 0.95 mmol, 2 M in CH<sub>2</sub>Cl<sub>2</sub>) was added dropwise to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (412 mg, 0.763 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and DMF (0.28 mL) at rt under Ar. The reaction mixture was stirred for 20 min, poured onto a mixture of ice and H<sub>2</sub>O (1:1, 30 mL) and diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The layers were separated and the organic layer was washed with cold H<sub>2</sub>O (2 x 30 mL) and brine (1 x 30 mL) and dried over MgSO<sub>4</sub>. Concentration *in vacuo* gave the desired bromide as a brown oil. This oil was taken up in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and DMF (1 mL). Compound **471Dii** (100 mg, 0.763 mmol), tetrabutylammonium bromide (111 mg, 0.526 mmol) and 4 Å sieves (600 mg) were added to this solution and the reaction was stirred under Ar for 4 d. The reaction was quenched with MeOH (2 mL), stirred for 0.5 h, diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and then filtered through a medium porosity fritted funnel, rinsing with CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The solvent was removed *in vacuo* and the resulting residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL). The organic solution was washed with sat. aq. NaHCO<sub>3</sub> (1 x 20 mL) and H<sub>2</sub>O (1 x 20 mL) and dried over MgSO<sub>4</sub>. Purification by flash chromatography on SiO<sub>2</sub> eluting with 50% EtOAc/hexanes gave 79 mg (33%) of **506A** as a white solid. HPLC: 99% at 4.56 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90%

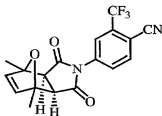
aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  902  $[M+H]^+$ .

**B. 4-[[3a*S*-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-5-( $\alpha$ -D-Glucopyranosyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (506B)**

Palladium hydroxide (62 mg, 20 wt.% Pd (dry basis) on carbon, wet) was added to a solution of **506A** (65 mg, 0.07 mmol) in EtOAc (2 mL) and the mixture was stirred under a hydrogen atmosphere introduced via a balloon. After 5 h, the reaction was complete as was evident by HPLC, so the mixture was filtered through a medium porosity fritted funnel rinsing with MeOH (2 mL) and concentrated *in vacuo*. The resulting residue was dissolved in MeOH (2 mL) and filtered through a Gelman Acrodise CR 13 mm syringe filter with a 0.45  $\mu$ M PTFE membrane. Concentration yielded 38 mg of **506B** as a white solid. HPLC: 90% at 2.16 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES):  $m/z$  543.20  $[M+H]^+$ . A 10 mg portion was recrystallized from MeOH:H<sub>2</sub>O to give crystals suitable for X-ray crystal diffraction studies to elucidate the exact stereochemistry of compound **506B** as referenced to the known fixed stereochemistry of the D-glucoside appendage.

**Example 507**

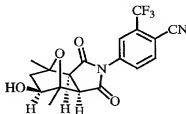
**(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (507)**



To 25 g (94.2 mmol) of compound **471A** was added neat 2,5-dimethylfuran (30 mL, 280 mmol), and the resulting slurry was heated to 60 °C for 1 to 3 h with mechanical agitation. The resulting slurry was cooled to 0-5 °C, and diluted with cold toluene (25 mL, 0-10 °C). The cold slurry was filtered under vacuum. The flask and filter cake were washed with cold toluene (2 x 25 mL), and the cake was deliquored with house vacuum. The precipitate was dried *in vacuo* to yield 31.3 g (91.6%) of a compound **507** as a tan solid. HPLC: 99.6%, 19.43 min (retention time) (Column: Zorbax™ SB-C18, 4.6 x 15 cm; Mobile Phase: 40% CH<sub>3</sub>CN/60% H<sub>2</sub>O w/ 0.1% v/v TFA, isocratic; Flow Rate: 1 mL/min; Detection:  $\lambda_{\text{max}}$  210 nm; Temperature: 30 °C; Injection Volume: 5  $\mu$ L).

### Example 508

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (508)

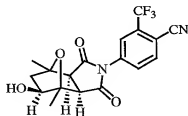


To THF (275 mL) that had been cooled to -3 °C was added compound **507** (55.0 g, 152 mmol), which resulted in a slurry. To the slurry was added borane methylsulfide (14.4 mL, 152 mmol), at a rate such that the temperature did not exceed 0 °C. The reaction mixture was slowly warmed to 20 °C over 2.5 h. The temperature of the reaction mixture was then returned to 0 °C, where upon phosphate buffer (1056 mL, pH 7) was carefully added at a rate to control the hydrogen gas evolution and maintain a temperature  $\leq$  20 °C. The resulting suspension was dissolved by adding ethanol (528 mL, 190 proof). At 15 °C, hydrogen peroxide (55 mL, 30 wt%) was added at a rate to maintain the temperature  $\leq$  20 °C. The homogeneous solution was left stirring for 12 h at 20 °C and pH 7.8, whereby crystallization occurred. The resulting slurry was collected by filtration and washed with water (4 X 100 mL) and methyl-*tert*-butyl ether (2 X 100 mL). Drying

*in vacuo* afforded 37.3 g (64.6%) of compound **508**. The aqueous mother liquor was extracted with ethyl acetate (3 X 500 mL). The combined rich organics were washed with 10 wt% aqueous sodium sulfite (1 X 100 mL), and 25 wt% aqueous sodium chloride (1 X 100 mL). The organics were dried over sodium sulfate, filtered, and concentrated to recover 8.9 g (15.4%) of compound **508**, and a third 11.5 g (20%) fraction of compound **508** was recovered from the methyl-*tert*-butyl ether cake wash. The above three solid samples of crude material were separately recrystallized from 190 proof ethanol (1 g / 10 mL) to afford a total of 35.6 g (61.7%) of compound **508** having a purity level of 98.7% as determined by HPLC analysis (conditions as below). A second crop of compound **508** was isolated from the mother liquor to afford 9.3 g (16.1%) of solid having a purity level of 98.4% as determined by HPLC analysis. The remaining mother liquor was purified by silica gel chromatography using 200 g of SiO<sub>2</sub> and eluting with 4 L of 50V% ethyl acetate and 50 V% heptane to yield 5.6 g (9.7%) of compound **508**, having a purity level of 94.0% as determined by HPLC analysis. HPLC conditions: 9.74 minute retention time on a YMC S5 ODS-AQ column (4.6 x 150 mm) using a gradient elution from 100% solvent A to 100% solvent B over 15 minutes at 1.0 mL/min. Solvent A = 95 V% water (0.01 M NH<sub>4</sub>OAc); 5 V% acetonitrile. Solvent B = 5 V% water (0.01 M NH<sub>4</sub>OAc); 95 V% acetonitrile. Dual wavelength detector set at 210 and 245 nm. MS (ES): *m/z* 381.11 [M+H]<sup>+</sup>.

#### Example 509

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (509)

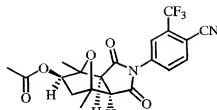
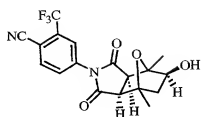


Compound **471A** (0.37 g, 1.4 mmol) and 2,5-dimethylfuran (0.73 mL, 6.9 mmol) were combined to form a slurry which was heated to 60 °C for 1 h. The reaction mixture

was cooled to  $-10\text{ }^{\circ}\text{C}$  and THF (1.0 mL) was added followed by the addition of borane tetrahydrofuran (2.1 mL, 1 M). The reaction mixture was stirred for 30 minutes at  $0\text{ }^{\circ}\text{C}$  and 30 minutes at  $+10\text{ }^{\circ}\text{C}$ . To the reaction mixture was added acetone (3.0 mL), and the resulting mixture was warmed to  $20\text{ }^{\circ}\text{C}$  and maintained at  $20\text{ }^{\circ}\text{C}$  for 1 h. To this solution was added sodium bicarbonate (1.5 mL, pH 9, 8 wt%) and the mixture was then cooled to  $5\text{ }^{\circ}\text{C}$  before adding hydrogen peroxide (0.3 mL, 30 wt%). Addition of hydrogen peroxide was exothermic bringing the temperature to  $20\text{ }^{\circ}\text{C}$ . A solution of sodium sulfite (4.0 mL, 10 wt%) was added at  $20\text{ }^{\circ}\text{C}$  resulting in an exotherm to  $30\text{ }^{\circ}\text{C}$ . The biphasic mixture was allowed to stand at  $25\text{ }^{\circ}\text{C}$  for 12 h. After the phases were separated, the aqueous waste was back extracted twice with ethyl acetate (5 mL) and the combined organic layers were washed with water (2 mL) followed by sodium chloride (2 mL, 25 wt%). The organic layers were concentrated *in vacuo* to yield a yellow oil which rapidly crystallized. To the crude product was added 190 proof ethanol (5.0 mL) and the mixture was heated to  $60\text{ }^{\circ}\text{C}$  to afford complete dissolution. Cooling to  $20\text{ }^{\circ}\text{C}$  for 17 h resulted in crystallization. The crystal slurry was collected by filtration, washed with heptane (5 mL), and dried at  $60\text{ }^{\circ}\text{C}$  under vacuum (30 in/Hg) to afford 0.23 g (44 %) of compound **509** having 93.1 HPLC Area%. HPLC conditions: 9.74 minute retention time on a YMC S5 ODS-AQ column (4.6 x 150 mm) using a gradient elution from 100% solvent A to 100% solvent B over 15 minutes at 1.0 mL/min. Solvent A = 95 V% water (0.01 M  $\text{NH}_4\text{OAc}$ ); 5 V% acetonitrile. Solvent B = 5 V% water (0.01 M  $\text{NH}_4\text{OAc}$ ); 95 V% acetonitrile. Detector set at 245 nm. MS (ES): m/z 381.11  $[\text{M}+\text{H}]^+$ .

#### Example 510

[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (510i) & [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[5-(Acetyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (510ii)



Compound **509** (4 mg), vinyl acetate (0.1 mL) and toluene (2 mL) were combined and 20 mg of each of the enzymes shown in Table 12 were added. The mixture was stirred with a magnetic stirring bar at rt in a 16 x 100 mm capped tube for the time period listed in Table 12. The enantioselective acetylation of the racemic mixture resulted in the formation of compound **510i** and the acetylated compound **510ii**. The enantiomeric purity of compound **510i** was determined by chiral HPLC (method below) and the results for each enzyme are as shown in Table 12. The resulting information was used to prepare a large scale batch of compounds **510i** & **510ii** as described below.

Table 12:

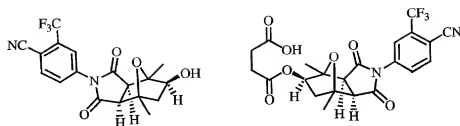
Enzyme	Supplier	Source	Time	Comp. 510i	Comp. 510i	Comp. 510i	Comp. 510ii
			H	mg/mL	% yield	% ee	mg/mL
AK-20	Amano	<i>Pseudomonas fluorescens</i>	15	0.74	39	100	1.02
AP-12	Amano	<i>Aspergillus niger</i>	144	1.10	58	55.4	0.74
PS-30	Amano	<i>Pseudomonas cepacia</i>	15	0.46	24	100	1.24
Acylase 30000	Amano	<i>Aspergillus</i>	15	0.51	27	12.2	1.26
Chirazyme L3	Boehringer	<i>Candida rugosa</i>	144	0.81	42	87.2	1.04
Lipase type VII	Sigma	<i>Candida rugosa</i>	144	0.74	39	100	1.06

To a 500 mL jacketed flask were added Amano lipase AK20 from *Pseudomonas fluorescens* (25 g), compound **509** (25 g), methyl-isobutyl-ketone (475 mL) and vinyl acetate (25 mL). The flask was maintained at 25°C with a circulating water bath and stirred with a magnetic stir bar. The incubation was continued for 42 h, at which point the enantiomeric excess of compound **510i** reached 100%. The solution was filtered through Whatman 4 filter paper to remove enzyme and the filter cake was washed with 50 mL methyl isobutyl ketone. The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc (50 mL) followed by the addition of heptane (50 mL). This solution was loaded onto a Phenomenex cartridge column (silica 800 g) in a Biotage 75L system and the column was eluted with 75% EtOAc / heptane at flow rate 110 mL/min. Fractions were collected (500 mL) which contained compound **510ii** and then the eluting solvent was changed to 100% EtOAc to elute off compound **510i**. The desired fractions were pooled and the solvent was removed *in vacuo* to yield 11.0 g of compound **510i**, (44%, 100%ee) and 12.10 g of compound **510ii** (44%). Compound **510i** was recrystallized from 95% EtOH (5 mL/g) in two crops to afford 9.61 g (38%) of compound **510i** as a white crystalline solid. Compounds **510i**: Chiral HPLC: 10.02 min (retention time) (CHIRALPAK AD 4.6 x 250 mm column; isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). HPLC: 99% at 2.45 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 [M+H]<sup>+</sup>.

#### Example 511

[3aR-(3α,4β,5β,7β,7α)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (511i) & Butanedioic acid, mono[3aS-(3α,4β,5β,7β,7α)]-[2-[4-cyano-3-(trifluoromethyl)phenyl]octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindol-5-yl]ester - (511ii)





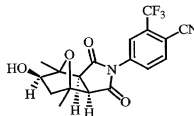
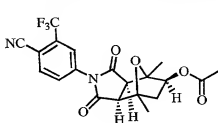
A mixture of the racemic compound **509** (10 mg), succinic anhydride (100 mg) and lipase AK-20 Amano (50 mg) in toluene or MTBE (5 mL) was stirred at rt for 20 hours. After 16 and 20 h, samples (0.1 mL) were taken out from each reaction mixture, evaporated, redissolved in acetonitrile (1 mL) and analyzed by reversed phase HPLC (YMC Pro-pack ODS-A, 3 $\mu$ , 15 X 0.6 cm, acetonitrile:water 20:80 to 90:10 in 12 min) to determine the area ratio of products compound **511i** (RT = 8.8 min) and compound **511ii** (RT = 9.9 min). A second sample (0.1 mL) of each reaction mixture was removed, evaporated and redissolved in 1 mL isopropyl alcohol-heptane (1:1) and analyzed by Chiral HPLC (Chiralpak AD, 25 X 0.46 cm, 20 °C, heptane:ethanol 85:15, 0.5 mL/min, UV 210 nm) to determine the % ee of compound **511i** (RT = 32.2 min) and compound **471Di** (RT = 34.8 min). After 20 h, the reaction mixtures were filtered off to separate the insoluble components (enzyme, etc.). The filtrates were washed with 5% aqueous NaHCO<sub>3</sub> (3 X 1 volume) and water (3 X 1 volume), evaporated *in vacuo* and analyzed by HPLC as described above. The results showed an average yield of 48% (theoretical max yield is 50%) and 100% ee for compound **511i**. Complete separation of compound **511ii** was achieved via the above described NaHCO<sub>3</sub> extraction. Table 13 gives the details of each reaction as determined by the methods described above. Compound **511i**: Chiral HPLC: 10.02 min; CHIRALPAK AD 4.6 x 250 mm column; isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min, 100% ee. HPLC: 99% at 2.45 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 [M+H]<sup>+</sup>.

Table 13.

Solvent	Solvent	Comp. 509	Lipase AK-20	Succinic Anhydride	Time	Comp. 511i	Comp. 511ii	Comp 511i	Comp 471Dii	Comp. 511i
	Vol., ml	mg	mg	mg	Hr	8.8 min	9.9 min	32.2 min	34.8 min	ce%
						Area Ratio	Area Ratio	%	%	
Toluene	5	10	50	100	16	53%	47%	93.1%	6.9%	86.2%
					20	54%	46%	96.0%	4.0%	92.0%
Toluene Wash NaHCO <sub>3</sub>						100%	0%	96.1%	3.9%	92.2%
MTBE	5	10	50	100	16	49%	51%	100.0%	0.0%	100.0%
					20	50%	50%	100.0%	0.0%	100.0%
MTBE Wash NaHCO <sub>3</sub>						100%	0%	100.0%	0.0%	100.0%

**Example 512**

**[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )-4-[5-(Acetyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (512i) & [3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (512ii)]**



A series of 50 mL flasks were arranged and enzymes (see Table 14 for enzyme type and amounts) were weighed into each followed by the addition of phosphate buffer (BF45, 5 mL, 100 mM, pH 7). A solution of compound **473** (5 mg) in DMSO (50  $\mu$ L) was added to each flask. The flasks were shaken at 200 rpm at 28 °C for 24 hours. After

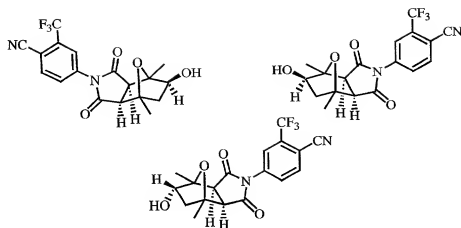
24 hours, the reaction mixtures were extracted with EtOAc (10 mL). A portion of the EtOAc extract (1 mL) was evaporated, redissolved in acetonitrile (1 mL) and analyzed by reversed phase HPLC (C-18, acetonitrile:water 20:80 to 90:10 in 12 min) to determine the area ratio of compound **512i** (RT = 11.0 min) and compound **512ii**, (RT = 8.9 min). Another portion of EtOAc extract (4 mL) was evaporated, redissolved in 1 mL isopropyl alcohol-heptane (1:1) and analyzed by chiral HPLC (Chiralpak AD, heptane:ethanol 85:15, 0.5 mL/min) to determine the % ee of the compound **512ii** (RT = 34.8 min) and compound **471Di** (RT = 32.2 min) in this system. Table 14 gives details for an array of different enzymes examined and the resulting yields and % ee for the desired products.

Table 14.

Enzyme	Supplier	Source	Enz Amt mg	Area Ratio by HPLC Comp. 512i	Comp. 512i	Exo-Alcohol Comp 471Di	Exo-Alcohol Comp. 511i	% ee of Comp 512ii
Lipase AP-12	Amano	Aspergillus niger	5	18%	82%	18.8%	81.2%	62.5%
Lipase AP-12	Amano	Aspergillus niger	25	50%	50%	41.0%	59.0%	17.9%
Lipase PS	Amano	Pseudomonas cepacia	5	20%	80%	31.8%	68.7%	37.4%
Lipase PS	Amano	Pseudomonas cepacia	25	46%	54%	40.2%	59.8%	19.6%
Acylase 150000	Amano	Aspergillus sp	5	30%	70%	52.0%	48.0%	-3.9%
Acylase 150001	Amano	Aspergillus sp	25	71%	29%	50.4%	49.6%	-0.8%
Newlase F	Amano	Rhizopus niveus	50	3%	97%	31.8%	68.7%	37.5%
Newlase F	Amano	Rhizopus niveus	100	3%	97%	25.7%	74.3%	48.9%
Acylase I	Sigma	Apergillus melleus	5	10%	90%	9.7%	90.3%	80.6%
Acylase I	Sigma	Apergillus melleus	25	38%	62%	10.9%	89.1%	78.3%
Esterase	Sigma	Porcine liver	5	76%	24%	36.0%	64.0%	27.9%

**Example 513**

[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (513i) & [3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (513ii) & (3 $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,7 $\beta$ ,7 $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (513iii)



A series of microbial biotransformation reactions were set up to generate compounds **513i**, **513ii** & **513iii**. The details of the reactions for several microorganisms are shown in Table 15 and a general procedure is described below. One thawed vial of the microbe (1 mL culture) was inoculated into sterile soybean-glucose media (10 mL) in a 50 mL flask. The microbes were grown by shaking at 200 rpm at 28°C for 40 h. A solution of compound **472** (10 mg in 100 µL DMSO) was added to each flask and the flasks were shaken at 200 rpm at 28 °C. At 24 and 48 h, 5 mL of the reaction mixtures were extracted by EtOAc (10 mL). A portion of EtOAc extract (1 mL) was evaporated, redissolved in acetonitrile (1 mL) and analyzed by reversed phase HPLC (C-18, acetonitrile: water 20:80 to 90:10 in 12 min) to determine the area ratio of compound **472** (RT = 11.2 min) and the product compounds **513i** (RT = 8.9 min), **513ii** (RT = 8.9 min) & **513iii** (RT = 9.6 min). A second portion of the EtOAc extract (4 mL) was evaporated, redissolved in isopropyl alcohol-heptane (1:1, 1 mL) and analyzed by chiral HPLC (Chiralpak AD, Heptane:Ethanol 85:15, 0.5 mL/min) to determine the % ee of compounds **513i** (RT = 32.2 min) compound **513ii** (RT = 34.8 min) in this system.

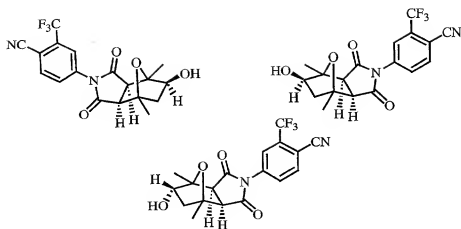
Table 15.

Microorganism	ID	Time Hrs	Analysis by Reversed Phase HPLC (Area Ratio)			Analysis for % ee by HPLC		% ee of
			Comp 513i	Comp 513ii	Comp 472	Comp 513i	Comp 513ii	Comp 513i
<i>Streptomyces sp</i>	SC1754	24	7%	0%	93%	96.9%	3.1%	93.9%
		48	12%	0%	88%	96.7%	3.3%	93.3%

<i>Streptomyces sp</i>	SC3740	24	1%	0%	99%	88.0%	12.0%	76.0%
		48	2%	0%	98%	85.8%	14.2%	71.7%
<i>Nocardia interforma</i>	ATCC 21072	24	5%	0%	95%	93.2%	6.8%	86.3%
		48	8%	0%	92%	92.6%	7.4%	85.1%
<i>Streptomyces antibioticus</i>	ATCC 14890	24	11%	1%	88%	95.7%	4.3%	91.4%
		48	48%	13%	39%	94.1%	5.9%	88.2%
<i>Streptomyces medicidicus</i>	ATCC 13278	24	1%	0%	99%	82.0%	18.0%	64.1%
		48	7%	0%	93%	79.4%	20.6%	58.8%
<i>Streptomyces griseus</i>	NRRL B8090	24	23%	0%	77%	85.0%	15.0%	70.0%
		48	28%	0%	72%	85.9%	14.1%	71.8%
<i>Amycolatopsis orientalis</i>	ATCC 43490	24	12%	1%	86%	81.3%	18.7%	62.5%
		48	25%	4%	71%	77.4%	22.6%	54.9%

**Example 514**

**[3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (514i) & [3aS-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (514ii) & (3a $\alpha$ ,4 $\beta$ ,5 $\alpha$ ,7 $\beta$ ,7a $\alpha$ )-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (514iii)**



A series of microbial biotransformation reactions were set up to generate compounds **514i**, **514ii** & **514iii**. The details of the reactions for several microorganisms are shown in Table 16 and a general procedure is described below. A 1 mL culture of *Streptomyces griseus* SC13971 from a frozen vial was used to inoculate 100 mL of medium (0.5% toasted nutrisoy, 2% glucose, 0.5% yeast extract, 0.5% K<sub>2</sub>HPO<sub>4</sub>, 0.5% NaCl, adjusted to pH 7 with 1N HCl (R. V. Smith and J. P. Rosazza, Arch. Biochem. Biophys., 161, 551-558 (1974)) in a 500 mL Erlenmeyer flask and the flask was incubated at 28°C at 200 rpm for 3 days. 10 mL of this culture was used to inoculate 100 mL of medium (as above) in a 500 mL Erlenmeyer flask and the flask was incubated at 28°C at 200 rpm for 1 day. For the filamentous fungi *Mucor rouxii* and *Cunninghamella echinulata*, 1 mL of spore suspension, prepared by washing a slant with 10 mL water, was used to inoculate 100 mL of medium (as above) in a 500 mL Erlenmeyer flask and the flask was incubated at 28° C at 200 rpm for 1 day. Compound **472** (30 mg in 1 mL methanol) was added to each culture and the incubations were continued for 6 to 10 days. Samples of 10 mL of the culture broth in each flask were removed and extracted with ethyl acetate (20 mL). Samples of 10 mL of the organic layers were each individually evaporated to dryness at 40 °C under a nitrogen stream. The residues were dissolved in 1.2 mL isopropanol and analyzed by reversed phase HPLC (YMC Pak ODS 150x6mm, 3 µ C-18, acetonitrile: water 20:80 to 90:10 in 12 min, 1 mL/min, 40 °C) to determine the concentration of compound **472** (RT = 11.2 min) and product compounds **514i** (RT = 8.9 min), **514ii** (RT = 8.9 min) & **514iii** (RT = 9.6 min). The same samples were analyzed

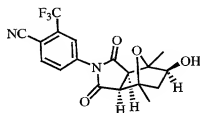
by chiral HPLC (Chiralpak AD, heptane:ethanol 85:15, 0.5 mL/min) to determine the % ee of compounds **514i** (RT = 32.2 min) compound **514ii** (RT = 34.8 min) in this system.

Table 16.

strain	SC	ATCC	time days	Comp. 472 mg/ml	Comp. 514i mg/ml	Comp 514i ee %	Comp514iii mg/ml
1. <i>Mucor rouxii</i>	13920	24905	3	0.30	0.01	100.00	0.000
			6	0.27	0.01	100.00	0.000
2. <i>Streptomyces griseus</i>	13971	13273	3	0.29	0.01	100.00	0.000
			6	0.30	0.01	100.00	0.000
3. <i>Cunninghamella echinulata</i>	16027	9244	3	0.34	0.02	100.00	0.002
			6	0.06	0.02	100.00	0.001
			10	0.16	0.02	100.00	0.001

### Example 515

#### [3aR-(3a $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (515)



Microbial transformation of compound **472** to compound **515** was conducted on a 3 L scale in a 5 L fermentor, using *Cunninghamella echinulata* SC 16027 (ATCC 9244) and a medium consisting of the following: 0.5% toasted nutrisoy, 2% glucose, 0.5% yeast extract, 0.5% K<sub>2</sub>HPO<sub>4</sub>, 0.5% NaCl, adjusted to pH 7 with 1N HCl (R. V. Smith and J. P. Rosazza, Arch. Biochem. Biophys., 161, 551-558 (1974)). The fermentor was batched with 0.05% SAG antifoam before sterilization. Spore inoculum was prepared by washing the spores from a 10 day slant culture of *Cunninghamella echinulata* SC 16027 (ATCC 9244) with 0.9% saline / 0.1% Tween 80. The inoculum stage was prepared by adding 1 mL of spore inoculum into 100 mL medium in a 500 mL flask, then the cultures were

grown at 28° C at 200 rpm for 1 day. 10% inoculum from the flask was blended in a sterile Waring blender and used to inoculate the sterile fermentor, containing 3 L of sterile media. The fermentor was run at 28°C at 600 rpm and 1 vvm aeration. A sterile solution of three antibiotics was added to the fermentor after inoculation; 12 mg of tetracycline chloride, 12 mg of kanamycin sulfate, and 60 mg of cephalexin hydrate in 10 mL of deionized water. After 22 hours of growth in the fermentor, a sterile substrate solution was added containing 0.75 g of compound **472** dissolved in 30 mL of methanol, this step was repeated two hours later for a total of 0.5 g/L of compound **472** in the bioconversion. The fermentation conditions were maintained at 28° C at 600 rpm and 1 vvm aeration. pH 6.5 was maintained by the automatic addition of 10% H<sub>2</sub>SO<sub>4</sub> or 10% NaOH. Periodically, 10 mL aseptic samples were taken and extracted with two 10 mL portions of ethyl acetate. The ethyl acetate layer was isolated, dried under a nitrogen stream at 40 °C, and the residue was dissolved in 2.0 mL of isopropyl alcohol. The samples were analyzed by reverse phase HPLC (method below) to determine the ratio of compound **472** and the product compound **515**. In addition, each sample was analyzed by chiral HPLC (method below) in order to determine the % ee of compound **515**. During the bioconversion process, a sterile solution of 30% cerelose and 1.5% yeast extract was fed into the reaction at ~5 mL / hour. After 114 h from the time of substrate addition, reverse phase HPLC analysis indicated the production of a 78% yield of compound **515**. Chiral HPLC analysis measured the % e.e. of compound **515** at 94.9%. The above process was repeated in another 3 L bioconversion, and the reaction was conducted at 28°C at 600 rpm, 1 vvm aeration, with 0.5 g/L of compound **472** input. After 44 h, this reaction gave a 80% yield of compound **515** with 95% e.e. The broth was filtered through a pad of HyFlo™ to provide a clarified fermentation broth. The broth was filtered through a pad of HyFlo™ to provide a clarified fermentation broth. Compound **515** was completely adsorbed onto 55 g of XAD-16 and extracted back into a 1:1 mixture of EtOAc and acetone (3 X 100 mL) or methyl-*tert*-butyl ether (3 X 100 mL). The solvent was removed *in vacuo* and the resulting residue was purified by silica pad (5 g), eluting with EtOAc. The desired fractions were collected and treated with activated carbon (0.5 g) to decolorize the solution and the solvent was removed *in vacuo* to



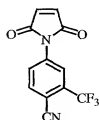
yield 1.27 g of compound **515**. Re-crystallization of this material from EtOAc/heptane (10 mL/20 mL) resulted 950 mg of crystalline compound **515** having 97% purity by reverse phase HPLC and 95% ee by chiral HPLC. Reverse Phase HPLC: YMC Pak ODS-A C18 column, 4.6 x 50 mm, eluting with a gradient of : 0 min 20% acetonitrile/80% 0.1% TFA in water, 12 min 90% acetonitrile/10% 0.1% TFA in water, 12.01-15 min 20% acetonitrile/80% 0.1% TFA in water, monitoring at 250 nm, 40°C, 5  $\mu$ L injection volume). Compound **515**: RT = 8.86 min. Chiral HPLC: CHIRALPAK OD 25x0.46 cm column; isocratic elution with 15% ethanol/85% heptane at 0.5 mL/min, 18 °C, monitoring at 220 nm, injection volume: 20  $\mu$ L. Compound **515**: RT = 36.5 min.

In an alternate recovery process, the fermentation broth (1L) from the above biohydroxylation reaction was filtered and the cake of cells was washed with 100 mL of water. Clear broth was extracted with ethyl acetate (2 X 600 mL) and the cake of cells was extracted with 400 mL of ethyl acetate. The combined ethyl acetate layers were concentrated and the resulting residue was dissolved in 5 mL of 1:1 heptane / ethyl acetate and loaded on to silica gel pad pad (70 g in 250 mL fritted glass filter). The silica gel pad was eluted with a gradient of 80 to 90% EtOAc/heptane. Fractions were collected and the fractions containing compound **515** were pooled. The solvent was removed *in vacuo* and resulting product was crystallized from EtOAc/heptane to give a 90% yield of compound **515** with 98% purity by reverse phase HPLC and 95% ee by chiral HPLC. Reverse Phase HPLC: YMC Pak ODS-A C18 column, 4.6 x 50 mm, eluting with a gradient of : 0 min 20% acetonitrile/80% 0.1% TFA in water, 12 min 90% acetonitrile/10% 0.1% TFA in water, 12.01-15 min 20% acetonitrile/80% 0.1% TFA in water, monitoring at 250 nm, 40°C, 5  $\mu$ L injection volume). Compound **472**: RT = 11.12 min. Compound **515**: RT = 8.86 min. Chiral HPLC: CHIRALPAK OD 25x0.46 cm column; isocratic elution with 15% ethanol/85% heptane at 0.5 mL/min, 18 °C, monitoring at 220 nm, injection volume: 20  $\mu$ L. Compound **472**: RT = 27.4 min. Compound **515**: RT = 36.5 min. Compound (**514iii**) RT = 39.1 min.

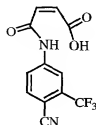
#### Example 516

#### 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (516B)

The following Example demonstrates preparation of an intermediate useful for preparing compounds of the formula I of the present invention.



**A. 3-(4-Cyano-3-trifluoromethylphenylcarbamoyl)acrylic acid (516A)**



5-amino-2-cyanobenzotrifluoride (210.6 mmol; 40.00 g) and butyl acetate (80 mL) were added to a 250 mL round bottom flask, followed by the addition of maleic anhydride (231.9 mmol, 23.20 g). The resulting suspension was heated to 60 °C for 3.5 h. The reaction mixture was cooled to 25 °C and then heptane (160 mL) was added dropwise over a period of 25 minutes. The resulting suspension was filtered and washed with a mixture of 4:1, heptane:butyl acetate (30 mL) and heptane (45 mL). The cake was dried *in vacuo* to give 60 g (95% yield) of compound **516A**.

**B. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile(516B)**

Compound **516A** (17.42 mmol, 5.000 g) was added to the reaction flask followed by the addition of zinc bromide (17.58 mmol, 3.960 g) and then toluene (50.00 mL, 43.25 g) was added to the mixture. The resulting suspension was stirred for 20 min. Hexamethyldisilazane (26.35 mmol, 5.560 mL, 4.253 g) was added to this

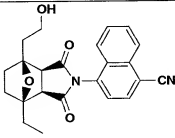
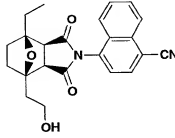
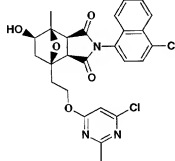
suspension which was then heated to 60 °C for 4.5 h. The reaction mixture was diluted with EtOAc (25 mL) and then poured into a 1N HCl solution (30 mL) at 25 °C. The organic phase was collected and the aqueous phase was extracted with EtOAc (15 mL). The organic phase was isolated, combined with the earlier organic phase and washed consecutively with saturated NaHCO<sub>3</sub> (15 mL), a mixture of 1:1 water:brine solution (15 mL) and brine (15 mL). The resulting solution was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to a 50 mL suspension. Heptane (125 mL) was added dropwise to this suspension with agitation. The resulting thicker suspension was filtered and washed with a mixture of 2:1 heptane:toluene (15 mL) and then heptane (15 mL) to give 4 g (85% yield) of compound **516B**. HPLC: 100% at 2.11 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

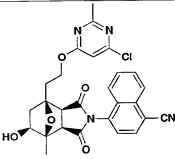
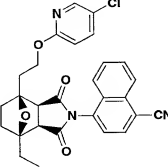
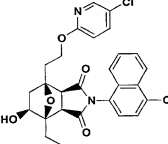
#### **Examples 517 to 746 and 751 to 753**

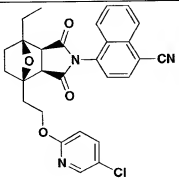
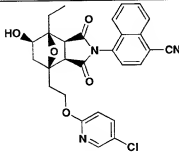
Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 517 to 746 and 751 to 753 have the structures shown in the following Table 17.

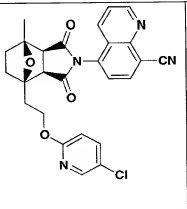
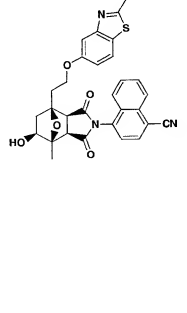
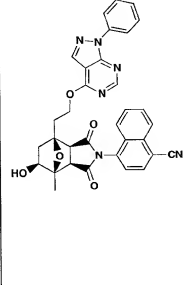
Table 17 also provides the compound name, retention time/molecular mass, and the procedure employed for preparation of these compounds. The chromatography techniques used to determine the compound retention times of **Table 17** are as follows: LC and LCMS were described in Examples 439 to 454 (Table 9). The molecular mass of the compounds listed in **Table 17**, where provided, was determined by MS (ES) by the formula  $m/z$ .

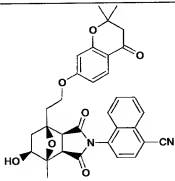
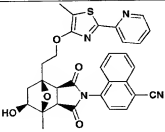
<b>Ex. No.</b>	<b><u>Compound Structure</u></b>	<b>Compound Name</b>	<b>Retention Time Min.</b>	<b>Pro. of Ex.</b>
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			<b>/</b> <b>Molecular</b> <b>Mass</b>	
<b>517</b>		[3aR-(3α,4β,7β,7α)]-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.84 LC [M + H] <sup>+</sup> = 391.16	245 & 461
<b>518</b>		[3aS-(3α,4β,7β,7α)]-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.84 LC [M + H] <sup>+</sup> = 391.16	245 & 461
<b>519</b>		[3aS-(3α,4β,5β,7β,7α)]-4-[7-[2-[(6-Chloro-2-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.04 LC [M + H] <sup>+</sup> = 519.0	243 & 244

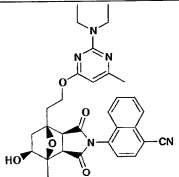
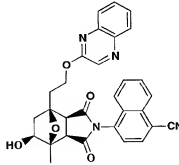
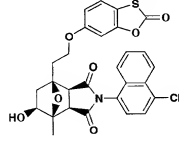
		naphthalenecarbonit rile		
520		[3aR- (3α,4β,5β,7β,7α)]- 4-[7-[2-[(6-Chloro-2- methyl-4- pyrimidinyl)oxy]ethy l]octahydro-5- hydroxy-4-methyl- 1,3-dioxo-4,7-epoxy- 2H-isoindol-2-yl]-1- naphthalenecarbonit rile	3.04 LC [M + H] <sup>+</sup> = 519.0	243 & 244
521		[3aR- (3α,4β,7β,7α)]-4-[4- [2-[(5-Chloro-2- pyridinyl)oxy]ethyl]- 7-ethyloctahydro-1,3- dioxo-4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile	3.90 LC [M + H] <sup>+</sup> = 502.28	245 & 461
522		[3aR- (3α,4β,5β,7β,7α)]- 4-[7-[2-[(5-Chloro-2- pyridinyl)oxy]ethyl]- 4-ethyloctahydro-5- hydroxy-1,3-dioxo- 4,7-epoxy-2H-isoindol-2-yl]-1- naphthalenecarbonit rile	3.37 LC [M + H] <sup>+</sup> = 518.28	435, 499 & 500

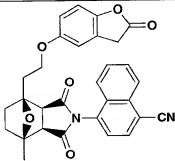
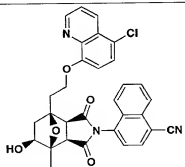
		4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
523		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.90 LC [M + H] <sup>+</sup> = 502.27	245 & 461
524		[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.40 LC [M + H] <sup>+</sup> = 518.27	435, 499 & 500

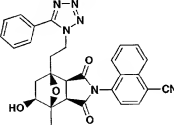
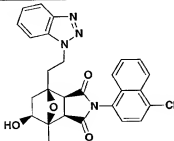
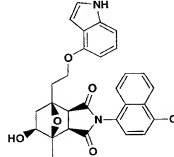
525		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-5-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.32 LC [M + H] <sup>+</sup> = 489.26	467
526		[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(2-methyl-5-benzothiazolyl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.36 LC [M + H] <sup>+</sup> = 540.0	243 & 244
527		[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-	3.35 LC [M + OAc] <sup>+</sup> = 644.8	243 & 244

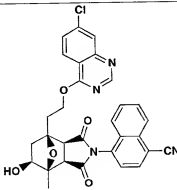
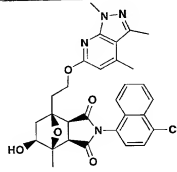
		yl]-1-naphthalenecarbonitrile		
528		[3aR-(3α,4β,5β,7β,7α)-4-[7-[2-[(3,4-Dihydro-2,2-dimethyl-4-oxo-2H-1-benzopyran-7-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.37 LC [M + OAc] <sup>-</sup> = 391.16	243 & 244
529		[3aR-(3α,4β,5β,7β,7α)-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[[5-methyl-2-(2-pyridinyl)-4-thiazolyl]oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.47 LC [M + H] <sup>+</sup> 566.9	243 & 244

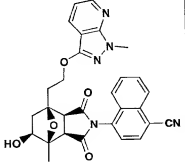
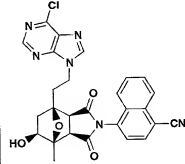
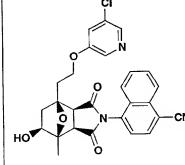


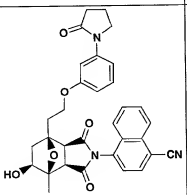
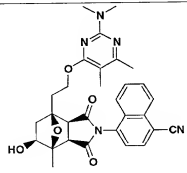
530		<p>[3aR-(3α,4β,5β,7β,7α)]-4-[7-[2-[(Diethylamino)-6-methyl-4-pyrimidinyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.47 LC [M + H]<sup>+</sup> = 556.1</p>	<p>243 &amp; 244</p>
531		<p>[3aR-(3α,4β,5β,7β,7α)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-(2-quinoxalinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.39 LC [M + H]<sup>+</sup> = 520.6</p>	<p>243 &amp; 244</p>
532		<p>[3aR-(3α,4β,5β,7β,7α)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(2-oxo-1,3-benzoxathiol-2-yl)]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.35 LC [M + OAc]<sup>-</sup> = 600.8</p>	<p>243 &amp; 244</p>

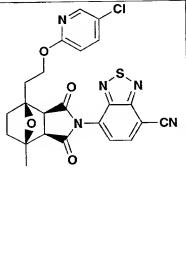
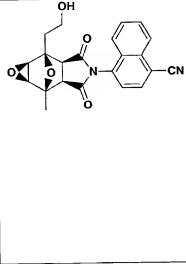
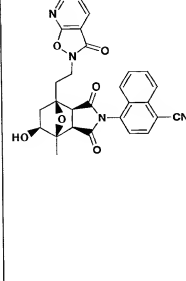
		5-yl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
533		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[4-[2-[(2,3-Dihydro-2-oxo-5-benzofuran)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.28 LC [M + OAc] <sup>+</sup> = 566.6	223 & 250
534		[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-[(5-Chloro-8-quinolyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.18 LC [M + H] <sup>+</sup> = 553.6	243 & 244

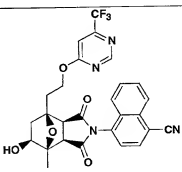
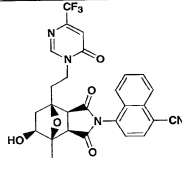
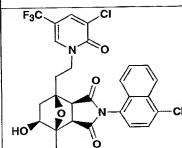
535		<p>[3aR- (3α,4β,5β,7β,7α)- 4-[Octahydro-5- hydroxy-4-methyl- 1,3-dioxo-7-[2-(5- phenyl-1H-tetrazol- 1-yl)ethyl]-4,7-epoxy- 2H-isoindol-2-yl]-1- naphthalenecarbonit rile</p>	<p>3.32 LC [M + H]<sup>+</sup> = 521.5</p>	<p>243 &amp; 244</p>
536		<p>[3aR- (3α,4β,5β,7β,7α)- 4-[7-[2-(1H-1,2,3- Benzotriazol-1- yl)ethyl]octahydro-5- hydroxy-4-methyl- 1,3-dioxo-4,7-epoxy- 2H-isoindol-2-yl]-1- naphthalenecarbonit rile</p>	<p>3.15 LC [M + H]<sup>+</sup> = 493.8</p>	<p>243 &amp; 244</p>
537		<p>[3aR- (3α,4β,5β,7β,7α)- 4-[Octahydro-5- hydroxy-7-[2-(1H- indol-4-yloxy)ethyl]- 4-methyl-1,3-dioxo- 4,7-epoxy-2H- isoindol-2-yl]-1-</p>	<p>3.05 LC [M]<sup>+</sup> = 507.6</p>	<p>243 &amp; 244</p>

		naphthalenecarbonit rile		
538		[3aR- (3α,4β,5β,7β,7α)- 4-[7-[2-[(7-Chloro-4- quinazolinyl)oxy]eth yl]octahydro-5- hydroxy-4-methyl- 1,3-dioxo-4,7-epoxy- 2H-isoindol-2-yl]-1- naphthalenecarbonit rile	3.33 LC [M + H] <sup>+</sup> = 555.2	243 & 244
539		[3aR- (3α,4β,5β,7β,7α)- 4-[Octahydro-5- hydroxy-4-methyl- 1,3-dioxo-7-[2-[(1,3,4- trimethyl-1H- pyrazolo[3,4- b]pyridin-6- yl)oxy]ethyl]-4,7- epoxy-2H-isoindol-2- yl]-1- naphthalenecarbonit rile	3.48 LC [M + H] <sup>+</sup> = 552.2	243 & 244

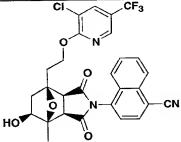
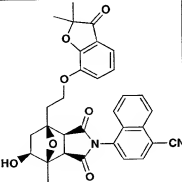
540		<p>[3aR-(3α,4β,5β,7β,7α)-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.08 LC [M + H]<sup>+</sup> = 524.2</p>	<p>243 &amp; 244</p>
541		<p>[3aR-(3α,4β,5β,7β,7α)-4-[7-[2-(6-Chloro-9H-purin-9-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.70 LC [M + H]<sup>+</sup> = 529.0</p>	<p>243 &amp; 244</p>
542		<p>[3aR-(3α,4β,5β,7β,7α)-4-[7-[2-[(5-Chloro-3-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-</p>	<p>3.17 LC [M + H]<sup>+</sup> = 504.1</p>	<p>243 &amp; 244</p>

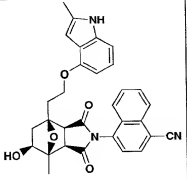
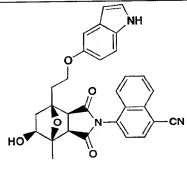
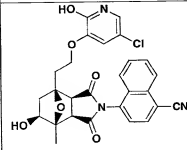
		4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile		
543		[3aR- (3α,4β,5β,7β,7α)- 4-[Octahydro-5- hydroxy-4-methyl- 1,3-dioxo-7-[2-[3-(2- oxo-1- pyrrolidinyl)phenoxy ]ethyl]-4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile	3.10 LC [M + H] <sup>+</sup> = 552.3	243 & 244
544		[3aR- (3α,4β,5β,7β,7α)- 4-[7-[2-[[2- (Dimethylamino)-5,6- dimethyl-4- pyrimidinyl]oxy]ethyl ]octahydro-5- hydroxy-4-methyl- 1,3-dioxo-4,7-epoxy- 2H-isoindol-2-yl]-1- naphthalenecarbonit rile	2.40 LC [M + H] <sup>+</sup> = 542.3	243 & 244

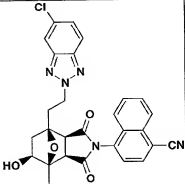
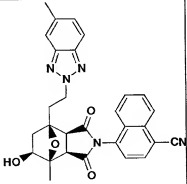
545		(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-7-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile	3.52 LC [M + H] <sup>+</sup> = 495.6	424A, 204, 482F & 482G
546		(1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-4-[Octahydro-2-(2-hydroxyethyl)-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isindol-4-yl]-1-naphthalenecarbonitrile	2.36 LC [M + H] <sup>+</sup> = 391.31	460 & 228
547		[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-(3-oxoisoxazolo[5,4-b]pyridin-2(3H)-yl)ethyl]-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile	2.92 LC [M + OAc] <sup>+</sup> = 568.6	243 & 244

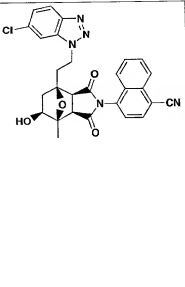
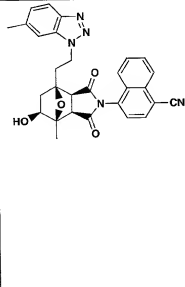
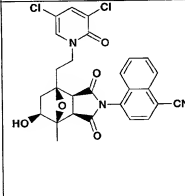
		rile		
548		[3aR-(3α,4β,5β,7β,7αα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	3.18 LC [M + OAc] <sup>+</sup> = 596.7	243 & 244
549		[3aR-(3α,4β,5β,7β,7αα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[6-oxo-4-(trifluoromethyl)-1(6H)-pyrimidinyl]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	2.94 LC [M + OAc] <sup>+</sup> = 596.5	243 & 244
550		[3aR-(3α,4β,5β,7β,7αα)]-4-[7-[2-[3-Chloro-2-oxo-5-	3.39 LC [M + OAc] <sup>+</sup> =	243 & 244

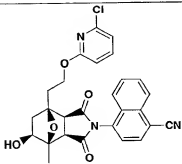
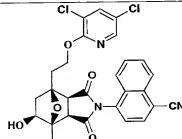


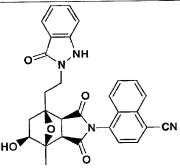
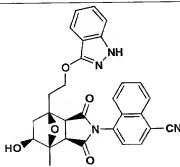
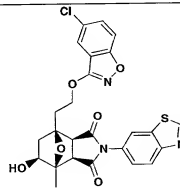
		(trifluoromethyl)- 1(2H)- pyridinyl]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	629.3	
551		[3aR-(3α,4β,5β,7β,7α)]-4-[7-[2-[[3-Chloro-5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.76 LC [M + OAc] <sup>-</sup> = 629.6	243 & 244
552		[3aR-(3α,4β,5β,7β,7α)]-4-[7-[2-[(2,3-Dihydro-2,2-dimethyl-3-oxo-7-benzofuranyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-	3.26 LC [M + OAc] <sup>-</sup> = 611.5	243 & 244

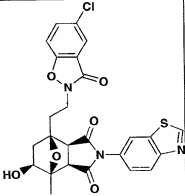
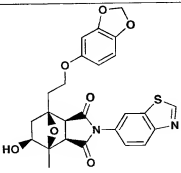
		2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
553		[3aR-(3α,4β,5β,7β,7α)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(2-methyl-1H-indol-4-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.16 LC [M + H] <sup>+</sup> = 522.5	243 & 244
554		[3aR-(3α,4β,5β,7β,7α)]-4-[Octahydro-5-hydroxy-7-[2-(1H-indol-5-yloxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.03 LC [M + H] <sup>+</sup> = 506.3	243 & 244
555		[3aR-(3α,4β,5β,7β,7α)]-4-[7-[2-[(5-Chloro-1,2-dihydro-2-oxo-3-pyridinyl)oxy]ethyl]o	2.85 LC [M + H] <sup>+</sup> = 520.5	243 & 244

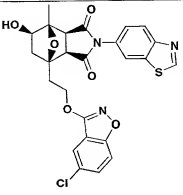
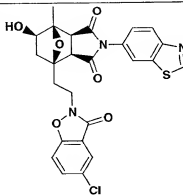
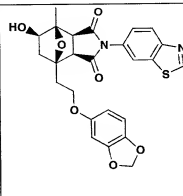
		ctahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rile		
556		[3aR-(3α,4β,5β,7β,7α)-4-[7-[2-(5-Chloro-2H-1,2,3-benzotriazol-2-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rile	3.53 LC [M + OAc] <sup>-</sup> = 586.3	243 & 244
557		[3aR-(3α,4β,5β,7β,7α)-4-[Octahydro-5-hydroxy-4-methyl-7-[2-(5-methyl-2H-1,2,3-benzotriazol-2-yl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rile	3.35 LC [M + H] <sup>+</sup> = 508.5	243 & 244

558		<p>[3aR- (3α,4β,5β,7β,7α)- 4-[7-[2-(6-Chloro-1H- 1,2,3-benzotriazol-1- yl)ethyl]octahydro-5- hydroxy-4-methyl- 1,3-dioxo-4,7-epoxy- 2H-isoindol-2-yl]-1- naphthalenecarbonit rile</p>	<p>3.32 LC [M + H]<sup>+</sup> = 528.3</p>	<p>243 &amp; 244</p>
559		<p>[3aR- (3α,4β,5β,7β,7α)- 4-[Octahydro-5- hydroxy-4-methyl-7- [2-(6-methyl-1H- 1,2,3-benzotriazol-1- yl)ethyl]-1,3-dioxo- 4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile</p>	<p>2.97 LC [M + H]<sup>+</sup> = 508.4</p>	<p>243 &amp; 244</p>
560		<p>[3aR- (3α,4β,5β,7β,7α)- 4-[7-[2-(3,5-Dichloro- 2-oxo-1(2H)- pyridinyl)ethyl]octah ydro-5-hydroxy-4- methyl-1,3-dioxo-4,7-</p>	<p>3.22 LC [M + H]<sup>+</sup> = 538.3</p>	<p>243 &amp; 244</p>

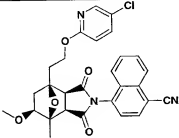
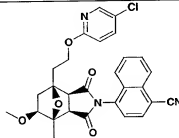
		epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
561		[3a <i>R</i> -(3α,4β,5β,7β,7α)-4-[7-[2-[(6-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.30 LC [M + H] <sup>+</sup> = 504.3	243 & 244
562		[3a <i>R</i> -(3α,4β,5β,7β,7α)-4-[7-[2-[(3,5-Dichloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.67 LC [M + H] <sup>+</sup> = 596.3	243 & 244

563		<p>[3aR-(3α,4β,5β,7β,7α)]-4-[7-[2-(1,3-Dihydro-3-oxo-2H-indazol-2-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.82 LC [M + H]<sup>+</sup> = 509.1</p>	<p>243 &amp; 244</p>
564		<p>[3aR-(3α,4β,5β,7β,7α)]-4-[Octahydro-5-hydroxy-7-[2-(1H-indazol-3-yloxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.19 LC [M + H]<sup>+</sup> = 509.2</p>	<p>243 &amp; 244</p>
565		<p>[3aR-(3α,4β,5β,7β,7α)]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]hexahydro-5-hydroxy-4-</p>	<p>3.21 LC [M + H]<sup>+</sup> = 526.2</p>	<p>481</p>

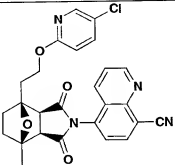
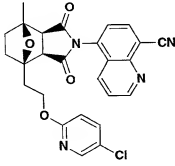
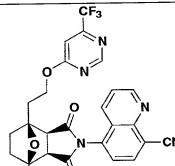
		methyl-4,7-epoxy-1H-isindole-1,3(2H)-dione		
566		[3aR-(3α,4β,5β,7β,7α)]-2-(6-Benzothiazolyl)-7-[2-(5-chloro-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isindole-1,3(2H)-dione	2.81 LC [M + H] <sup>+</sup> = 526.2	481
567		[3aR-(3α,4β,5β,7β,7α)]-7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]-2-(6-benzothiazolyl)hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isindole-1,3(2H)-dione	2.80 LC [M + H] <sup>+</sup> = 495.2	481

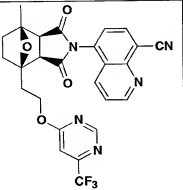
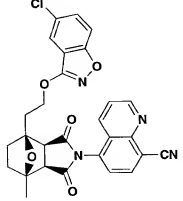
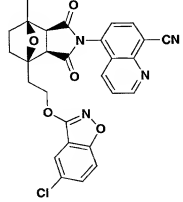
568		<p>[3aS-(3α,4β,5β,7β,7α)-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isindole-1,3(2H)-dione</p>	<p>3.21 LC [M + H]<sup>+</sup> = 526.1</p>	481
569		<p>[3aS-(3α,4β,5β,7β,7α)-2-(6-Benzothiazolyl)-7-[2-(5-chloro-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isindole-1,3(2H)-dione</p>	<p>2.84 LC [M + H]<sup>+</sup> = 391.16</p>	481
570		<p>[3aS-(3α,4β,5β,7β,7α)-7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]-2-(6-benzothiazolyl)hexahydro-5-hydroxy-4-</p>	<p>2.82 LC [M + H]<sup>+</sup> = 495.2</p>	481

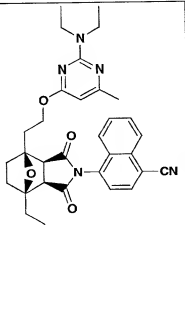
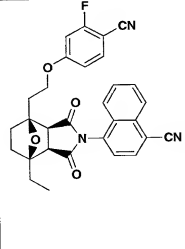
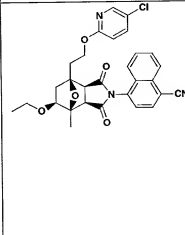


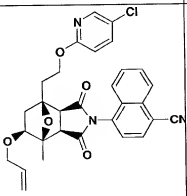
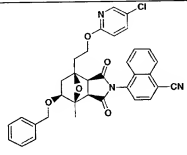
		methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione		
571		(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.64 & 3.76 atropisomers LCMS [M + H] <sup>+</sup> = 518.19	491
572		[3aR-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.50 LC [M + H] <sup>+</sup> = 518.28	491

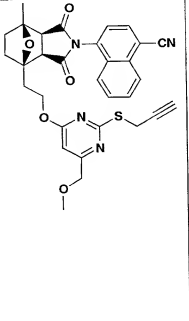
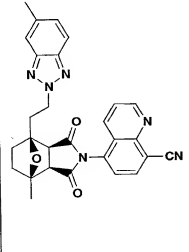
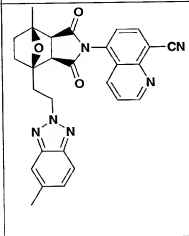
573		<p>[3aR-(3α,4β,7β,7α)]-4-[4-Ethyloctahydro-7-[2-(3-methoxyphenoxy)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>7.49 &amp; 7.75 atropisomers LC HRMS [M + CH<sub>3</sub>-CO<sub>2</sub>]<sup>+</sup> = 555.2144</p>	<p>245C, 461 &amp; 462</p>
574		<p>[3aR-(3α,4β,7β,7α)]-4-[4-[2-(3,5-Dimethylphenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>8.10 &amp; 8.31 atropisomers HRMS [M + CH<sub>3</sub>CO<sub>2</sub>]<sup>+</sup> = 553.2363</p>	<p><u>245C,</u> <u>461 &amp;</u> <u>462</u></p>
575		<p>[3aR-(3α,4β,7β,7α)]-4-[4-[2-[(2,3-Dihydro-1H-inden-5-yl)oxy]ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>8.17 &amp; 8.37 atropisomers HRMS [M + CH<sub>3</sub>CO<sub>2</sub>]<sup>+</sup> = 565.2326</p>	<p>245C, 461 &amp; 462</p>

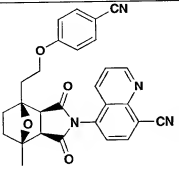
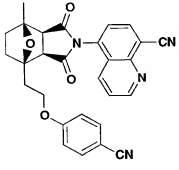
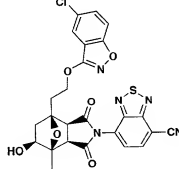
		rule		
576		[3aR-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.45 LC [M + H] <sup>+</sup> = 489.0	467 & 487
577		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.45 LC [M + H] <sup>+</sup> = 488.99	467 & 487
578		[3aR-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[Octahydro-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.25 LC [M + H] <sup>+</sup> = 524.0	467 & 487

579		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-5-[Octahydro-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile</p>	<p>3.45 LC [M + H]<sup>+</sup> = 523.98</p>	<p>467 &amp; 487</p>
580		<p>[3aR-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-5-[4-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile</p>	<p>3.66 LC [M + H]<sup>+</sup> = 529.16</p>	<p>467 &amp; 487</p>
581		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-5-[4-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile</p>	<p>3.66 LC [M + H]<sup>+</sup> = 529.16</p>	<p>467 &amp; 487</p>

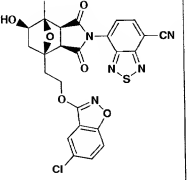
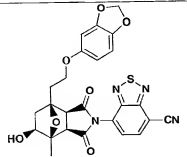
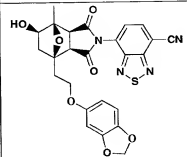
582		<p>[3aR-(3α,4β,7β,7α)]-4-[4-[2-[[2-(Diethylamino)-6-methyl-4-pyrimidinyl]oxy]ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>5.85 &amp; 6.06 atropisomers LC [M + H]<sup>+</sup> = 554.26</p>	<p>245C, 461 &amp; 462</p>
583		<p>[3aR-(3α,4β,7β,7α)]-4-[4-[2-(4-Cyano-3-fluorophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>7.23 &amp; 7.50 atropisomers HRMS [M - H]<sup>-</sup> = 508.1682</p>	<p>245C, 461 &amp; 462</p>
584		<p>[3aR-(3α,4β,5β,7β,7α)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-5-ethoxyoctahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-</p>	<p>3.60 LC [M + H]<sup>+</sup> = 532.23</p>	<p>223, 495 &amp; 496</p>

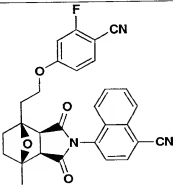
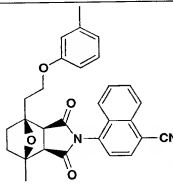
		naphthalenecarbonit rile		
585		[3aR-(3α,4β,5β,7β,7α)-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-1,3-dioxo-5-(2-propenyloxy)-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonit rile	3.68 LC [M + H] <sup>+</sup> = 544.23	491
586		[3aR-(3α,4β,5β,7β,7α)-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-1,3-dioxo-5-(phenylmethoxy)-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonit rile	3.63 LC [M + H] <sup>+</sup> = 594.26	491

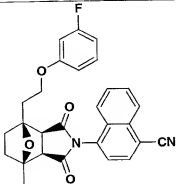
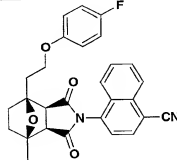
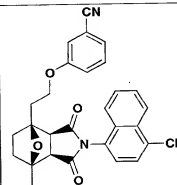
587		<p>[3a<i>S</i>- (3α,4β,7β,7α)]-4- [Octahydro-4-[2-[[6- (methoxymethyl)-2- (2-propynylthio)-4- pyrimidinyl]oxy]ethyl ]-7-methyl-1,3-dioxo- 4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile</p>	<p>4.02 LC [M + H]<sup>+</sup> = 567.31</p>	<p>491</p>
588		<p>[3a<i>R</i>- (3α,4β,7β,7α)]-5- [Octahydro-4-methyl- 7-[2-(5-methyl-2H- 1,2,3-benzotriazol-2- yl)ethyl]-1,3-dioxo- 4,7-epoxy-2H- isoindol-2-yl]-8- quinolinecarbonitrile</p>	<p>3.37 LC [M + H]<sup>+</sup> = 493.24</p>	<p>467 &amp; 487</p>
589		<p>[3a<i>S</i>- (3α,4β,7β,7α)]-5- [Octahydro-4-methyl- 7-[2-(5-methyl-2H- 1,2,3-benzotriazol-2- yl)ethyl]-1,3-dioxo- 4,7-epoxy-2H- isoindol-2-yl]-8-</p>	<p>3.37 LC [M + H]<sup>+</sup> = 493.24</p>	<p>467 &amp; 487</p>

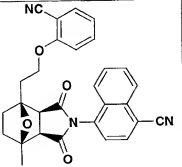
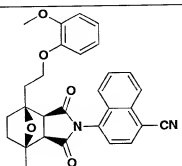
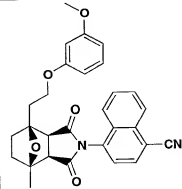
590		quinolinecarbonitrile [3aR-(3α,4β,7β,7α)-5-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile]	3.14 LC $[M + H]^+ = 479.22$	467 & 487
591		[3aS-(3α,4β,7β,7α)-5-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile]	3.14 LC $[M + H]^+ = 479.22$	467 & 487
592		[3aR-(3α,4β,5β,7β,7α)-7-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile]	3.38 LC $[M + H]^+ = 552.12$	482

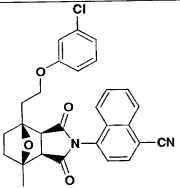
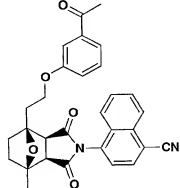
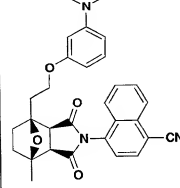


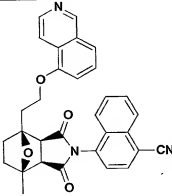
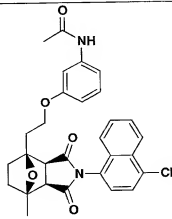
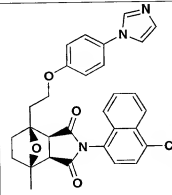
593		<p>[3a<i>S</i>- (3α,4β,5β,7β,7α)- 7-[7-[2-[(5-Chloro- 1,2-benzisoxazol-3- yl)oxy]ethyl]octahydr o-5-hydroxy-4- methyl-1,3-dioxo-4,7- epoxy-2H-isindol-2- yl]-2,1,3- benzothiadiazole-4- carbonitrile</p>	<p>3.39 LC [M + H]<sup>+</sup> = 552.10</p>	482
594		<p>[3a<i>R</i>- (3α,4β,5β,7β,7α)- 7-[7-[2-(1,3- Benzodioxol-5- yloxy)ethyl]octahydr o-5-hydroxy-4- methyl-1,3-dioxo-4,7- epoxy-2H-isindol-2- yl]-2,1,3- benzothiadiazole-4- carbonitrile</p>	<p>3.00 LC [M + H]<sup>+</sup> = 521.15</p>	482
595		<p>[3a<i>S</i>- (3α,4β,5β,7β,7α)- 7-[7-[2-(1,3- Benzodioxol-5- yloxy)ethyl]octahydr o-5-hydroxy-4-</p>	<p>2.99 LC [M + H]<sup>+</sup> = 521.14</p>	482

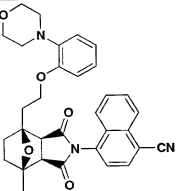
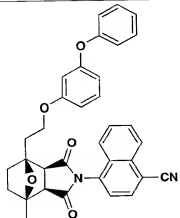
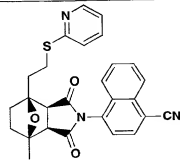
		methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile		
596		[3aR-(3α,4β,7β,7α)-4-[4-[2-(4-Cyano-3-fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.76 LCMS [M + H] <sup>+</sup> = 496.2	496
597		[3aR-(3α,4β,7β,7α)-4-[Octahydro-4-methyl-7-[2-(3-methylphenoxy)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.79 LCMS [M + H] <sup>+</sup> = 467.2	496

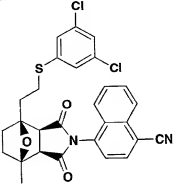
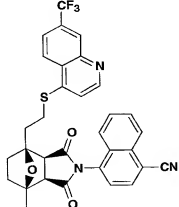
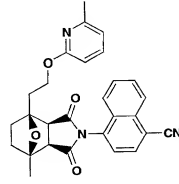
598		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.01 LCMS [M + H] <sup>+</sup> = 471.2	496
599		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(4-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.98 LCMS [M + H] <sup>+</sup> = 471.2	496
600		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(3-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.88 LCMS [M + H] <sup>+</sup> = 478.2	496

601		<p>[3aR-(3α,4β,7β,7α)]-4-[4-(2-(2-Cyanophenoxy)ethyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.42 LCMS [M + H]<sup>+</sup> = 478.2</p>	496
602		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-(2-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.83 LCMS [M + H]<sup>+</sup> = 483.2</p>	496
603		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.14 LCMS [M + H]<sup>+</sup> = 483.2</p>	496

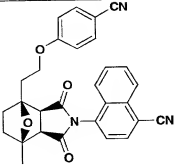
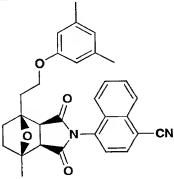
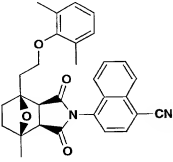
604		<p>[3aR-(3α,4β,7β,7α)]-4-[4-[2-(3-Chlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.09 LCMS [M + H]<sup>+</sup> = 487.2</p>	496
605		<p>[3aR-(3α,4β,7β,7α)]-4-[4-[2-(3-Acetylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.20 LCMS [M + H]<sup>+</sup> = 495.2</p>	496
606		<p>[3aR-(3α,4β,7β,7α)]-4-[4-[2-(3-(Dimethylamino)phenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.94 LCMS [M + H]<sup>+</sup> = 496.2</p>	496

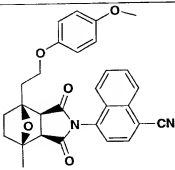
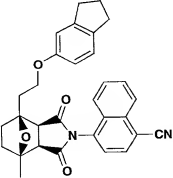
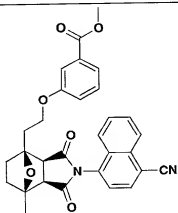
607		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-(5-isoquinolinyl)ethoxy]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.89 LCMS [M + H]<sup>+</sup> = 504.2</p>	496
608		<p>N-[3-[2-[3aR-(3α,4β,7β,7α)]-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenylacetamide</p>	<p>1.97 LCMS [M + H]<sup>+</sup> = 510.6</p>	496
609		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-[4-(1H-imidazol-1-yl)phenoxy]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.81 LCMS [M + H]<sup>+</sup> = 519.6</p>	496

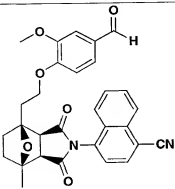
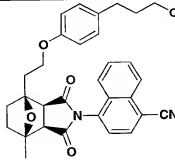
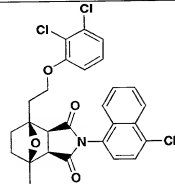
610		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-7-[2-(4-morpholinyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.16 LCMS [M + H]<sup>+</sup> = 538.2</p>	496
611		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(3-phenoxyphenoxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.89 LCMS [M + H]<sup>+</sup> = 545.2</p>	496
612		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(2-pyridinylthio)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.91 LCMS [M + H]<sup>+</sup> = 469.6</p>	496

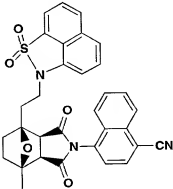
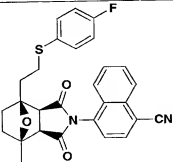
613		<p>[3aR-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[4-2-[(3,5-Dichlorophenyl)thio]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.53 LCMS [M + H]<sup>+</sup> = 537.1</p>	496
614		<p>[3aR-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[[7-(trifluoromethyl)-4-quinolinyl]thio]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.49 LCMS [M + H]<sup>+</sup> = 588.2</p>	496
615		<p>[3aR-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[Octahydro-4-methyl-7-[2-[(6-methylpyridinyl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.79 LCMS [M + H]<sup>+</sup> = 467.5</p>	496



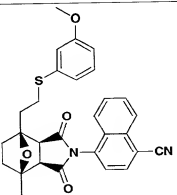
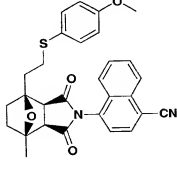
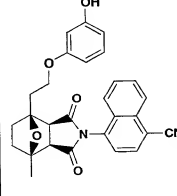
		rule		
616		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rule	1.98 LCMS [M + H] <sup>+</sup> = 478.2	496
617		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(3,5-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rule	1.80 LCMS [M + H] <sup>+</sup> = 481.2	496
618		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(2,6-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-	1.88 LCMS [M + H] <sup>+</sup> = 481.2	496

		naphthalenecarbonit rile		
619		[3a <i>R</i> - (3aα,4β,7β,7aα)]-4- [Octahydro-4-[2-(4- methoxyphenoxy)eth yl]-7-methyl-1,3- dioxo-4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile	1.50 LCMS [M + H] <sup>+</sup> = 483.2	496
620		[3a <i>R</i> - (3aα,4β,7β,7aα)]-4-[4- [2-[(2,3-Dihydro-1H- inden-5- yl)oxy]ethyl]octahydr o-7-methyl-1,3-dioxo- 4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile	2.14 LCMS [M + H] <sup>+</sup> = 493.3	496
621		3-[2-[[3a <i>R</i> - (3aα,4β,7β,7aα)]-2-(4- Cyano-1- naphthalenyl)octahy dro-7-methyl-1,3- dioxo-4,7-epoxy-4H- isoindol-4-	3.99 LCMS [M + H] <sup>+</sup> = 511.2	496

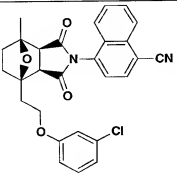
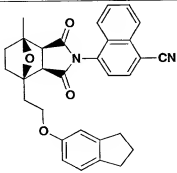
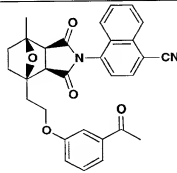
		yl]ethoxy]benzoic acid, methyl ester		
622		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(4-Formyl-2-methoxyphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.01 LCMS [M + H] <sup>+</sup> = 511.2	496
623		[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-[4-(3-hydroxypropyl)phenylethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.93 LCMS [M + H] <sup>+</sup> = 511.3	496
624		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(2,3-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-	1.79 LCMS [M + H] <sup>+</sup> = 521.1	496

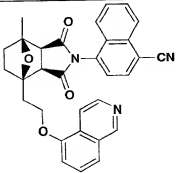
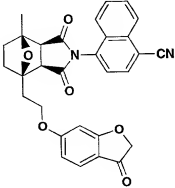
		epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
625		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(1,1-Dioxido-2H-naphtho[1,8-cd]isothiazol-2-yl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.69 LCMS [M + H] <sup>+</sup> = 564.2	496
626		[3aR-(3α,4β,7β,7α)]-4-[4-[2-[(4-Fluorophenyl)thio]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.03 LCMS [M + H] <sup>+</sup> = 487.2	496

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627		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-[(3-methoxyphenyl)thio]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.02 LCMS [M + H]<sup>+</sup> = 499.2</p>	496
628		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-[(4-methoxyphenyl)thio]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>1.99 LCMS [M + H]<sup>+</sup> = 499.2</p>	496
629		<p>[3aR-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-(3-hydroxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.27 LCMS [M + H]<sup>+</sup> = 469.2</p>	496

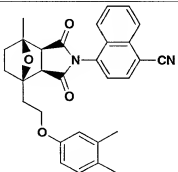
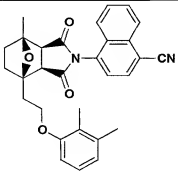
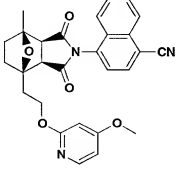
630		<p>[3aR-(3α,4β,7β,7α)]-4-[4-[2-[(4-Cyanophenyl)amino]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.56 LCMS [M + H]<sup>+</sup> = 477.2</p>	496
631		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-(3,5-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.10 LCMS [M + H]<sup>+</sup> = 481.2</p>	496
632		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-(3-methylphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-</p>	<p>3.56 LCMS [M + H]<sup>+</sup> = 483.2</p>	496

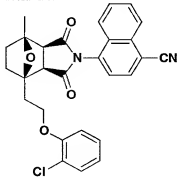
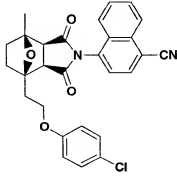
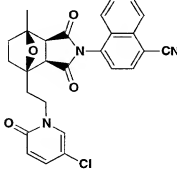
		naphthalenecarbonit rile		
633		[3aS-(3α,4β,7β,7α)]-4-[4-[2-(3-Chlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rile	4.03 LCMS [M + H] <sup>+</sup> = 487.1	496
634		[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(2,3-Dihydro-1H-inden-5-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rile	4.15 LCMS [M + H] <sup>+</sup> = 493.2	496
635		[3aS-(3α,4β,7β,7α)]-4-[4-[2-(3-Acetylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-	3.65 LCMS [M + H] <sup>+</sup> = 495.2	496

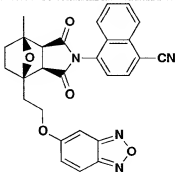
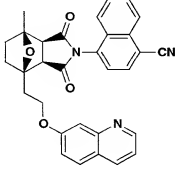
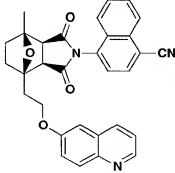
		naphthalenecarbonit rile		
636		[3aS-(3α,4β,7β,7α)-4-[Octahydro-4-[2-(5-isoquinolinyl)oxy]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.67 LCMS [M + H] <sup>+</sup> = 504.2	496
637		[3aS-(3α,4β,7β,7α)-4-[4-[2-[(2,3-Dihydro-3-oxo-6-benzofuranyl)oxy]ethoxy]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.90 LCMS [M + H] <sup>+</sup> = 509.2	496

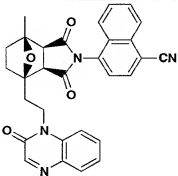
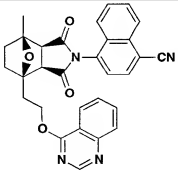


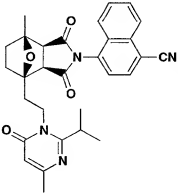
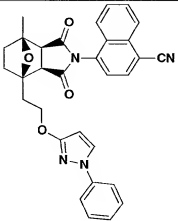
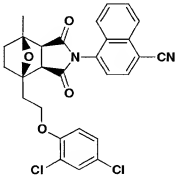
638		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[4-[2-(2,3-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.80 LCMS [M + H]<sup>+</sup> = 521.1</p>	496
639		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(3-phenoxyphenoxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.54 LCMS [M + H]<sup>+</sup> = 545.2</p>	496
640		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(4-pyrimidinyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.13 LCMS [M + H]<sup>+</sup> = 455.2</p>	496

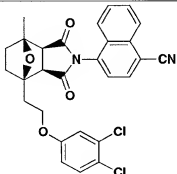
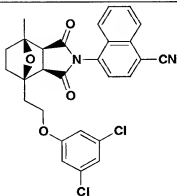
<b>641</b> 	<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-(3,4-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.19 LCMS [M + H]<sup>+</sup> = 481.2</p>	<p>496</p>
<b>642</b> 	<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-(2,3-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.80 LCMS [M + H]<sup>+</sup> = 481.2</p>	<p>496</p>
<b>643</b> 	<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-[(4-methoxy-2-pyridinyl)oxy]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-</p>	<p>2.72 LCMS [M + H]<sup>+</sup> = 484.2</p>	<p>496</p>

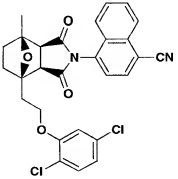
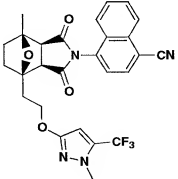
		naphthalenecarbonit rile		
644		[3aS- (3α,4β,7β,7α)]-4-[4- [2-(2- Chlorophenoxy)ethyl ]octahydro-7-methyl- 1,3-dioxo-4,7-epoxy- 2H-isindol-2-yl]-1- naphthalenecarbonit rile	2.63 LCMS [M + H] <sup>+</sup> = 487.1	496
645		[3aS- (3α,4β,7β,7α)]-4-[4- [2-(4- Chlorophenoxy)ethyl ]octahydro-7-methyl- 1,3-dioxo-4,7-epoxy- 2H-isindol-2-yl]-1- naphthalenecarbonit rile	4.07 LCMS [M + H] <sup>+</sup> = 487.1	496
646		[3aS- (3α,4β,7β,7α)]-4-[4- [2-(5-Chloro-2-oxo- 1(2H)- pyridinyl)ethyl]octah ydro-7-methyl-1,3- dioxo-4,7-epoxy-2H- isindol-2-yl]-1-	4.13 LCMS [M + H] <sup>+</sup> = 488.1	496

647		naphthalenecarbonitrile [3aS-(3α,4β,7β,7α)]-4-[4-(2-(2,1,3-Benzoxadiazol-5-yloxy)ethyl)]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.15 LCMS [M + H] <sup>+</sup> = 495.2	496
648		[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(7-quinolinyl-oxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.93 LCMS [M + H] <sup>+</sup> = 504.2	496
649		[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(6-quinolinyl-oxy)ethyl]-4,7-epoxy-2H-	4.01 LCMS [M + H] <sup>+</sup> = 504.2	496

		isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)		
650		[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(2-oxo-1(2H)-quinoxalinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.33 LCMS [M + H] <sup>+</sup> = 505.2	496
651		[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(4-quinazolinylloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.39 LCMS [M + H] <sup>+</sup> = 505.2	496

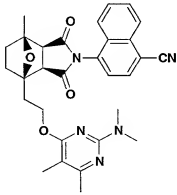
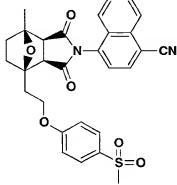
652		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-7-[2-[4-methyl-2-(1-methylethyl)-6-oxo-1(6H)-pyrimidinyl]ethyl]-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.72 LCMS [M + H]<sup>+</sup> = 511.3</p>	496
653		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[(1-phenyl-1H-pyrazol-3-yl)oxy]ethyl]-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)</p>	<p>3.48 LCMS [M]<sup>+</sup> = 519.2</p>	496
654		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-(2,4-dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.85 LCMS [M + H]<sup>+</sup> = 521.1</p>	496

		epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
655		[3aS-(3α,4β,7β,7α)]-4-[4-[2-(3,4-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.86 LCMS [M + H] <sup>+</sup> = 521.1	496
656		[3aS-(3α,4β,7β,7α)]-4-[4-[2-(3,5-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.47 LCMS [M + H] <sup>+</sup> = 521.1	496

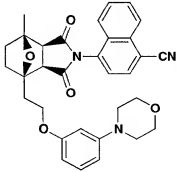
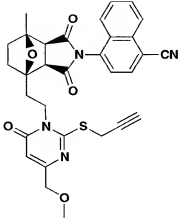
657		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[2-(2,5-Dichlorophenoxy)ethyloctahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.33 LCMS [M + H]<sup>+</sup> = 521.1</p>	496
658		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[Octahydro-4-methyl-7-[2-[[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)</p>	<p>3.87 LCMS [M + H]<sup>+</sup> = 525.2</p>	496

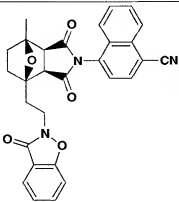
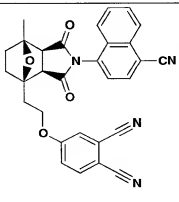
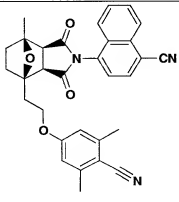
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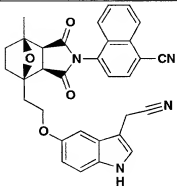
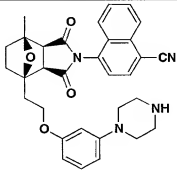
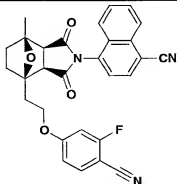


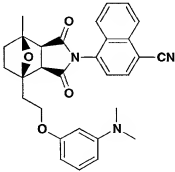
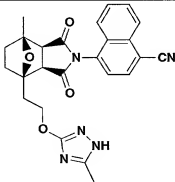
659		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(Dimethylamino)-5,6-dimethyl-4-pyrimidinyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)</p>	<p>2.71 LCMS [M + H]<sup>+</sup> = 526.2</p>	496
660		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-7-[2-[4-(methylsulfonyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>2.91 LCMS [M + H]<sup>+</sup> = 531.2</p>	496

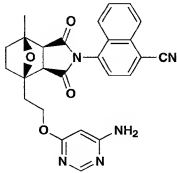
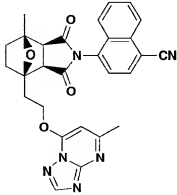
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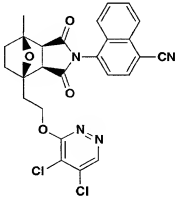
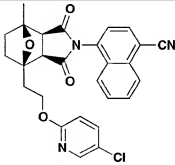
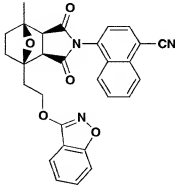
661		<p>[3aS-(3α,4β,7β,7α)-4-[Octahydro-4-methyl-7-[2-[3-(4-morpholinyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)</p>	<p>3.78 LCMS [M + H]<sup>+</sup> = 538.2</p>	496
662		<p>[3aS-(3α,4β,7β,7α)-4-[Octahydro-4-[2-[4-(methoxymethyl)-6-oxo-2-(2-propynylthio)-1(6H)-pyrimidinyl]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)</p>	<p>4.18 LCMS [M + H]<sup>+</sup> = 569.2</p>	496

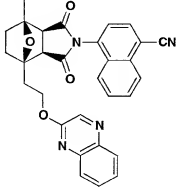
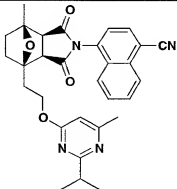
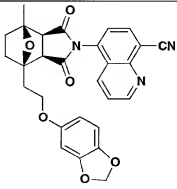
663		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.18 LCMS [M + H]<sup>+</sup> = 494.2</p>	496
664		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isindol-4-yl]ethoxy]-1,2-benzenedicarbonitrile</p>	<p>4.30 LCMS [M + H]<sup>+</sup> = 503.1</p>	496
665		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[4-[2-(4-Cyano-3,5-dimethylphenoxy)ethyloctahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-</p>	<p>4.13 LCMS [M + H]<sup>+</sup> = 506.2</p>	496

		naphthalenecarbonit rile		
666		[3aS- (3α,4β,7β,7α)]-5-[2- [2-(4-Cyano-1- naphthalenyl)octahy dro-7-methyl-1,3- dioxo-4,7-epoxy-4H- isoindol-4-yl]ethoxy]- 1H-indole-3- acetonitrile, trifluoroacetate (1:1)	3.36 LCMS [M + H] <sup>+</sup> = 531.2	496
667		[3aS- (3α,4β,7β,7α)]-4- [Octahydro-4-methyl- 1,3-dioxo-7-[2-[3-(1- piperazinyl)phenoxy] ethyl]-4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile, trifluoroacetate (1:1)	3.81 LCMS [M + H] <sup>+</sup> = 537.2	496
668		[3aS- (3α,4β,7β,7α)]-4-[4- [2-(4-Cyano-3- fluorophenoxy)ethyl] octahydro-7-methyl- 1,3-dioxo-4,7-epoxy-	2.89 LCMS [M + H] <sup>+</sup> = 496.2	496

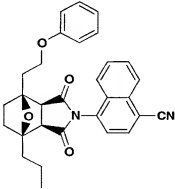
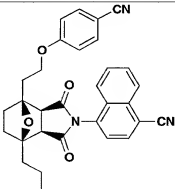
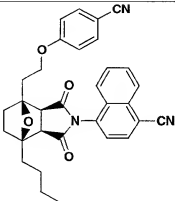
		2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
669		[3aS-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-[3-(Dimethylamino)phenoxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.37 LCMS [M + H] <sup>+</sup> = 496.2	496
670		[3aS-(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[Octahydro-4-methyl-7-[2-[(5-methyl-1H-1,2,4-triazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.26 LCMS [M + H] <sup>+</sup> = 458.2	496

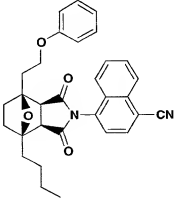
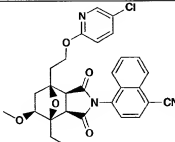
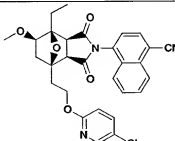
671		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(6-Amino-4-pyrimidinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)</p>	<p>2.97 LCMS [M + H]<sup>+</sup> = 470.2</p>	496
672		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-7-[2-[(5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)</p>	<p>3.45 LCMS [M + H]<sup>+</sup> = 509.2</p>	496

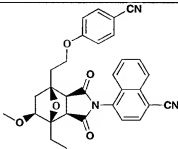
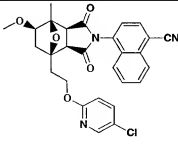
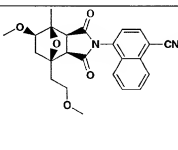
673		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(4,5-Dichloro-3-pyridazinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.79 LCMS [M + H]<sup>+</sup> = 523.1</p>	496
674		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.86 LCMS [M + H]<sup>+</sup> = 488.4</p>	496
675		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.78 LCMS [M + H]<sup>+</sup> = 494.41</p>	496

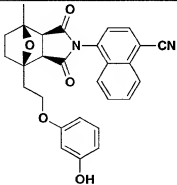
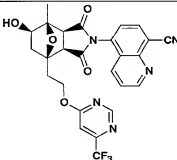
676		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(2-quinoxalinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.83 LCMS [M + H]<sup>+</sup> = 505.43</p>	496
677		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-7-[2-[[6-methyl-2-(1-methylethyl)-4-pyrimidinyl]oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.52 LCMS [M + H]<sup>+</sup> = 511.49</p>	496
678		<p>[3aS-(3α,4β,7β,7α)]-5-[4-[2-(1,3-Benzodioxoloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-</p>	<p>3.327 LC [M + H]<sup>+</sup> = 498.24</p>	467 & 487

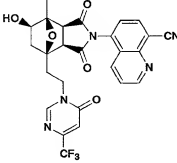
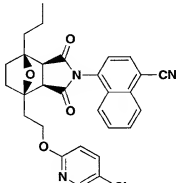
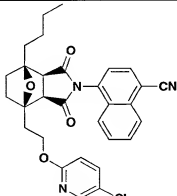


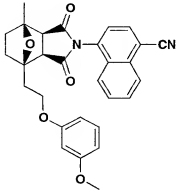
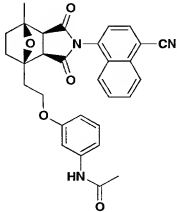
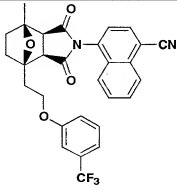
		quinolinecarbonitrile		
679		[3aR-(3α,4β,7β,7α)]-4-[Octahydro-1,3-dioxo-4-(2-phenoxyethyl)-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.77 & 8.01 atropisomer rs LC [M + H] <sup>+</sup> = 481.4	501
680		[3aR-(3α,4β,7β,7α)]-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.42 & 7.68 atropisomer rs LC [M + H] <sup>+</sup> = 506.38	501
681		[3aR-(3α,4β,7β,7α)]-4-[4-Butyl-7-[2-(4-cyanophenoxy)ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.69 & 7.92 atropisomer rs LC [M + H] <sup>+</sup> = 520.38	502

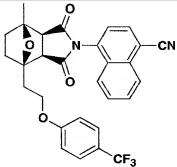
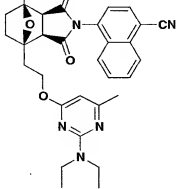
682		<p>[3aR-(3α,4β,7β,7α)]-4-[4-Butyloctahydro-1,3-dioxo-7-(2-phenoxyethyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>8.02 &amp; 8.23 atropisome rs LC [M + H]<sup>+</sup> = 495.33</p>	502
683		<p>[3aR-(3α,4β,5β,7β,7α)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)</p>	<p>7.31 &amp; 7.55 atropisome rs LC [M + H]<sup>+</sup> = 532.3</p>	504
684		<p>[3aS-(3α,4β,5β,7β,7α)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-</p>	<p>7.31 &amp; 7.55 atropisome rs LC [M + H]<sup>+</sup> = 532.3</p>	504

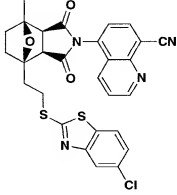
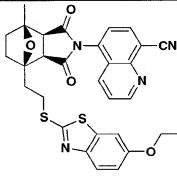
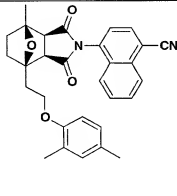
		naphthalenecarbonit rile, trifluoroacetate (1:1)		
685		[3aR- (3α,4β,5β,7β,7α)]- 4-[7-[2-(4- Cyanophenoxy)ethyl] -4-ethyloctahydro-5- methoxy-1,3-dioxo- 4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile	6.84 & 7.10 atropisome rs LC [M + H] <sup>+</sup> = 522.33	504
686		[3aS- (3α,4β,5β,7β,7α)]- 4-[7-[2-[(5-Chloro-2- pyridinyl)oxy]ethyl]o ctahydro-5-methoxy- 4-methyl-1,3-dioxo- 4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile	3.37 & 3.52 atropisome rs LC [M + H] <sup>+</sup> = 518.16	491
687		[3aS- (3α,4β,5β,7β,7α)]- 4-[Octahydro-5- methoxy-7-(2- methoxyethyl)-4-	2.57 & 2.75 atropisome rs LC [M + H] <sup>+</sup> =	491

		methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	421.18	
688		[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-(3-hydroxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.38 LCMS [M + H] <sup>+</sup> = 469.38	496
689		[3aS-(3α,4β,5β,7β,7α)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.833 LC [M + H] <sup>+</sup> = 540.17	485, 486, 487 & 488

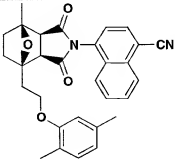
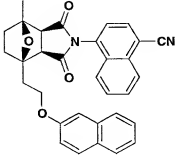
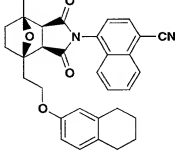
690		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,5<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[6-oxo-4-(trifluoromethyl)-1(6H)-pyrimidinyl]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile</p>	<p>2.59 LC [M + H]<sup>+</sup> = 540.16</p>	<p>485, 486, 487 &amp; 488</p>
691		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>7.91 &amp; 8.15 atropisomers LC [M + H]<sup>+</sup> = 516.25</p>	<p>501</p>
692		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[4-Butyl-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-</p>	<p>8.18 &amp; 8.39 atropisomers LC [M + H]<sup>+</sup> = 530.28</p>	<p>502</p>

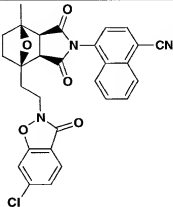
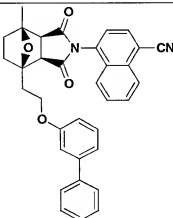
		naphthalenecarbonit rile		
693		[3aS- (3α,4β,7β,7α)]-4- [Octahydro-4-[2-(3- methoxyphenoxy)eth yl]-7-methyl-1,3- dioxo-4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile	3.97 LCMS [M + H] <sup>+</sup> = 483.1	496
694		<i>N</i> -[3-[2-[3aS- (3α,4β,7β,7α)]-2-(4- Cyano-1- naphthalenyl)octahy dro-7-methyl-1,3- dioxo-4,7-epoxy-4H- isoindol-4- yl]ethoxy]phenylacet amide	3.42 LCMS [M + H] <sup>+</sup> = 510.1	496
695		[3aS- (3α,4β,7β,7α)]-4- [Octahydro-4-methyl- 1,3-dioxo-7-[2-[3- (trifluoromethyl)phe noxy]ethyl]-4,7- epoxy-2H-isoindol-2- yl]-1-	3.83 LCMS [M + H] <sup>+</sup> = 521.1	496

		naphthalenecarbonit rile		
696		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rile	3.86 LCMS [M + H] <sup>+</sup> = 521.2	496
697		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-[2-[(Diethylamino)-6-methyl-4-pyrimidinyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit rile	3.63 LCMS [M + H] <sup>+</sup> = 540.2	496

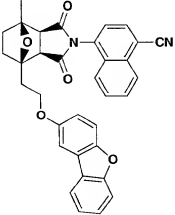
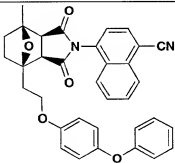
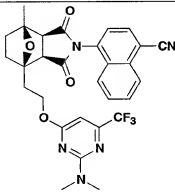
698		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(5-Chloro-2-benzothiazolyl)thio]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.15 LCMS [M]<sup>+</sup>= 560.0</p>	496
699		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(6-Ethoxy-2-benzothiazolyl)thio]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.15 LCMS [M + H]<sup>+</sup>= 570.1</p>	496
700		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-(2,4-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-</p>	<p>3.71 LCMS [M + H]<sup>+</sup>= 481.2</p>	496

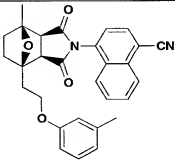
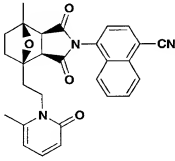


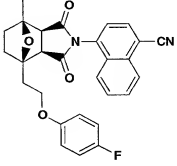
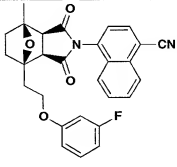
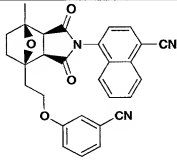
		naphthalenecarbonit rile		
701		[3aS- (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4- [2-(2,5- Dimethylphenoxy)et hyl]octahydro-7- methyl-1,3-dioxo-4,7- epoxy-2H-isoindol-2- yl]-1- naphthalenecarbonit rile	3.79 LCMS [M + H] <sup>+</sup> = 481.2	496
702		[3aS- (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4- [Octahydro-4-methyl- 7-[2-(2- naphthalenyloxy)eth yl]-1,3-dioxo-4,7- epoxy-2H-isoindol-2- yl]-1- naphthalenecarbonit rile	2.66 LCMS [M + H] <sup>+</sup> = 503.2	496
703		[3aS- (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4- [Octahydro-4-methyl- 1,3-dioxo-7-[2- [(5,6,7,8-tetrahydro- 2-	2.72 LCMS [M + H] <sup>+</sup> = 507.2	496

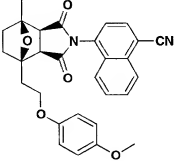
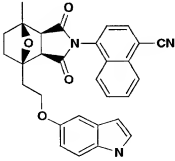
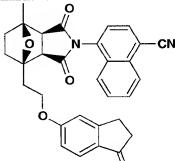
		naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
704		[3aS-(3α,4β,7β,7α)]-4-[4-[2-(6-Chloro-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.71 LCMS [M + H] <sup>+</sup> = 528.1	496
705		[3aS-(3α,4β,7β,7α)]-4-[4-[2-([1,1'-Biphenyl]-3-yloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.03 LCMS [M + H] <sup>+</sup> = 529.2	496

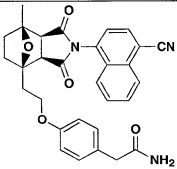
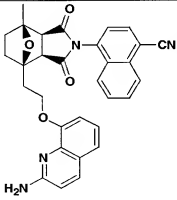
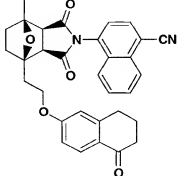
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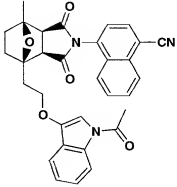
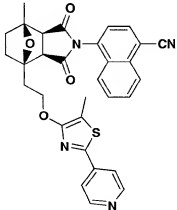
706		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-(2-Dibenzofuranyloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.51 LCMS [M + H]<sup>+</sup> = 543.2</p>	496
707		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(4-phenoxyphenoxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.73 LCMS [M + H]<sup>+</sup> = 545.2</p>	496
708		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(2-(Dimethylamino)-6-(trifluoromethyl)-4-pyrimidinyl]oxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.15 LCMS [M + H]<sup>+</sup> = 566.2</p>	496

		yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)		
709		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-methyl-7-[2-(3-methylphenoxy)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.17 LCMS [M + H] <sup>+</sup> = 466.5	496
710		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-methyl-7-[2-(6-methyl-2-oxo-1(2H)-pyridinyl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.41 LCMS [M + H] <sup>+</sup> = 468.2	496

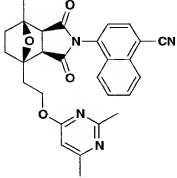
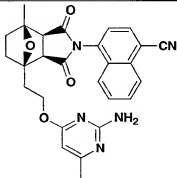
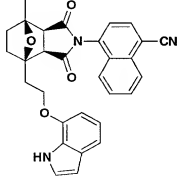
711		<p>[3aS-(3α,4β,7β,7α)]-4-[4-(2-(4-Fluorophenoxy)ethyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.10 LCMS [M + H]<sup>+</sup> = 471.2</p>	496
712		<p>[3aS-(3α,4β,7β,7α)]-4-[4-(2-(3-Fluorophenoxy)ethyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.56 LCMS [M + H]<sup>+</sup> = 471.2</p>	496
713		<p>[3aS-(3α,4β,7β,7α)]-4-[4-(2-(3-Cyanophenoxy)ethyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>4.28 LCMS [M + H]<sup>+</sup> = 478.2</p>	496

714		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-(4-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.58 LCMS [M + H]<sup>+</sup> = 483.2</p>	496
715		<p>[3aS-(3α,4β,7β,7α)]-4-[Octahydro-4-[2-(1H-indol-5-yloxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.40 LCMS [M + H]<sup>+</sup> = 492.2</p>	496
716		<p>[3aS-(3α,4β,7β,7α)]-4-[4-[2-[(2,3-Dihydro-1-oxo-1H-inden-5-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.20 LCMS [M + H]<sup>+</sup> = 507.2</p>	496

		rile		
717		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]benzeneacetamide	3.26 LCMS [M + H] <sup>+</sup> = 510.2	496
718		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-[2-[(2-Amino-8-quinolinyloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)]	2.77 LCMS [M + H] <sup>+</sup> = 519.2	496
719		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-	2.88 LCMS [M + H] <sup>+</sup> = 521.2	496

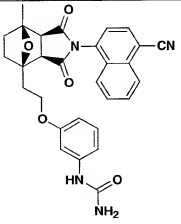
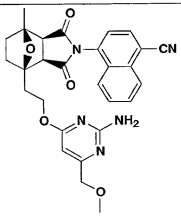
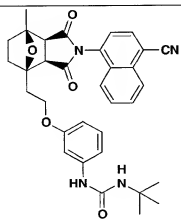
		isoindol-2-yl]-1-naphthalenecarbonitrile		
720		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-1-Acetyl-3-[2-[2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]-1H-indole	4.03 LCMS [M + H] <sup>+</sup> = 534.2	496
721		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-methyl-7-[2-[[5-methyl-2-(4-pyridinyl)-4-thiazolyl]oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	4.02 LCMS [M + H] <sup>+</sup> = 551.2	496

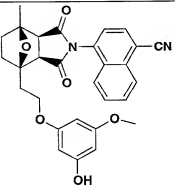
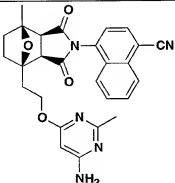


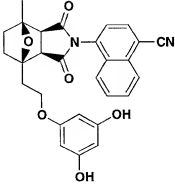
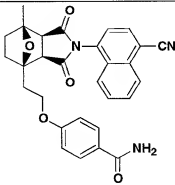
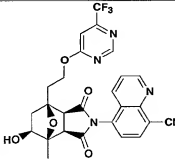
722		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[4-[2-[(2,6-Dimethyl-4-pyrimidinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.74 LCMS [M + H]<sup>+</sup> = 483.2</p>	496
723		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[4-[2-[(2-Amino-6-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile</p>	<p>3.71 LCMS [M + H]<sup>+</sup> = 484.2</p>	496
724		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-4-[4-[2-(1H-indol-7-yl)oxy]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-</p>	<p>4.23 LCMS [M + H]<sup>+</sup> = 492.2</p>	496

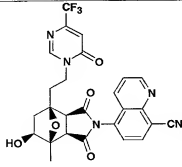
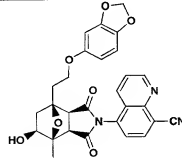
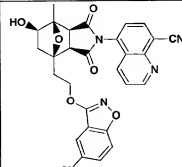
		naphthalenecarbonit rile		
725		[3aS- (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4- [Octahydro-4-methyl- 7-[2-(7-methyl-3-oxo- 1,2-benzisoxazol- 2(3H)-yl)ethyl]-1,3- dioxo-4,7-epoxy-2H- isoindol-2-yl]-1- naphthalenecarbonit rile	3.02 LCMS [M + H] <sup>+</sup> = 508.2	496
726		[3aS- (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4- [Octahydro-4-[2-[5- hydroxy-3-(2- hydroxyethyl)-1H- indol-1-yl]ethyl]-7- methyl-1,3-dioxo-4,7- epoxy-2H-isoindol-2- yl]-1- naphthalenecarbonit rile	2.94 LCMS [M + H] <sup>+</sup> = 536.2	496

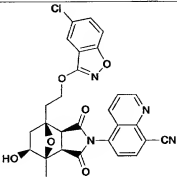
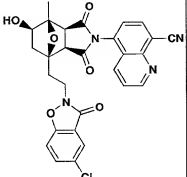
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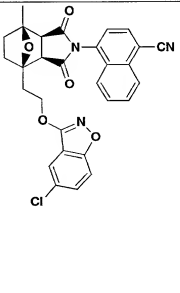
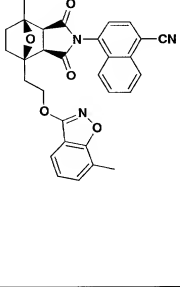
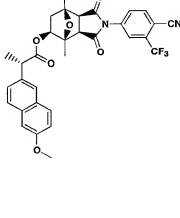
727		<i>N</i> -[3-[2-[[3a <i>S</i> -(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4 <i>H</i> -isoindol-4-yl]ethoxy]phenyl]urea	4.26 LCMS [ <i>M</i> + <i>H</i> ] <sup>+</sup> = 511.2	496
728		[3a <i>S</i> -(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-4-[4-[2-[[2-Amino-6-(methoxymethyl)-4-pyrimidinyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2 <i>H</i> -isoindol-2-yl]-1-naphthalenecarbonitrile	4.18 LCMS [ <i>M</i> + <i>H</i> ] <sup>+</sup> = 514.2	496
729		<i>N</i> -[3-[2-[[3a <i>S</i> -(3a $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7a $\alpha$ )]-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4 <i>H</i> -isoindol-4-yl]ethoxy]phenyl]- <i>N</i> '-	3.13 LCMS [ <i>M</i> + <i>H</i> ] <sup>+</sup> = 567.2	496

		(1,1-dimethylethyl)urea		
730		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[Octahydro-4-[2-(3-hydroxy-5-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile	4.22 LCMS [M + H] <sup>+</sup> = 499.2	496
731		[3aS-(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-4-[4-[2-[(6-Amino-2-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isindol-2-yl]-1-naphthalenecarbonitrile	4.19 LCMS [M + H] <sup>+</sup> = 484.2	496

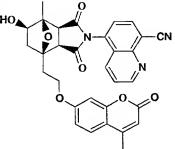
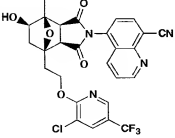
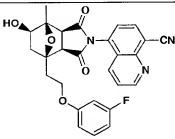
732		<p>[3aS- (3α,4β,7β,7α)]-4-[4- [2-(3,5- Dihydroxyphenoxy)et hyl]octahydro-7- methyl-1,3-dioxo-4,7- epoxy-2H-isindol-2- yl]-1- naphthalenecarbonit rile</p>	<p>3.73 LCMS [M + H]<sup>+</sup> = 485.1</p>	496
733		<p>[3aS- (3α,4β,7β,7α)]-4-[2- [2-(4-Cyano-1- naphthalenyl)octahy dro-7-methyl-1,3- dioxo-4,7-epoxy-4H- isindol-4- yl]ethoxy]benzamide</p>	<p>4.11 LCMS [M + H]<sup>+</sup> = 496.2</p>	496
734		<p>[3aR- (3α,4β,5β,7β,7α)]- 5-[Octahydro-5- hydroxy-4-methyl- 1,3-dioxo-7-[2-[[6- (trifluoromethyl)-4- pyrimidinyl]oxy]ethy l]-4,7-epoxy-2H- isindol-2-yl]-8- quinolinecarbonitrile</p>	<p>2.847 LC [M + H]<sup>+</sup> = 540.14</p>	485, 486, 487 & 488

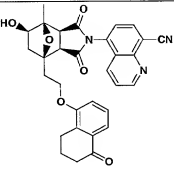
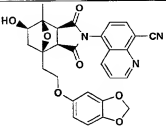
735		<p>[3aR-(3<math>\alpha</math>,4<math>\beta</math>,5<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[6-oxo-4-(trifluoromethyl)-1(6H)-pyrimidinyl]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile</p>	<p>2.577 LCMS [M + H]<sup>+</sup> = 540.14</p>	<p>485, 486, 487 &amp; 488</p>
736		<p>[3aR-(3<math>\alpha</math>,4<math>\beta</math>,5<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-5-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile</p>	<p>2.867 LCMS [M + H]<sup>+</sup> = 514.16</p>	<p>485, 486, 487 &amp; 488</p>
737		<p>[3aS-(3<math>\alpha</math>,4<math>\beta</math>,5<math>\beta</math>,7<math>\beta</math>,7<math>\alpha</math>)]-5-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-</p>	<p>3.24 LCMS [M + H]<sup>+</sup> = 545.12</p>	<p>485, 486, 487 &amp; 488</p>

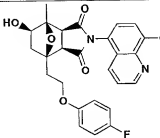
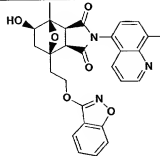
		epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile		
738		[3aR-(3α,4β,5β,7β,7α)-5-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.25 LCMS [M + H] <sup>+</sup> = 545.12	485, 486, 487 & 488
739		[3aS-(3α,4β,5β,7β,7α)-5-[7-[2-(5-Chloro-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.863 LCMS [M + H] <sup>+</sup> = 545.12	485, 486, 487 & 488

740		<p>[3aS- (3α,4β,7β,7α)]-4-[4- [2-[(6-Chloro-1,2- benzisoxazol-3- yl)oxy]ethyl]octahydr o-7-methyl-1,3-dioxo- 4,7-epoxy-2H- isindol-2-yl]-1- naphthalenecarbonit rile</p>	<p>4.04 LCMS [M + H]<sup>+</sup> = 528.1</p>	496
741		<p>[3aS- (3α,4β,7β,7α)]-4- [Octahydro-4-methyl- 7-[2-[(7-methyl-1,2- benzisoxazol-3- yl)oxy]ethyl]-1,3- dioxo-4,7-epoxy-2H- isindol-2-yl]-1- naphthalenecarbonit rile</p>	<p>3.94 LCMS [M + H]<sup>+</sup> = 508.1</p>	496
742		<p>(αS)-6-Methoxy-α- methyl-2- naphthaleneacetic acid, [3aR- (3α,4β,5β,7β,7α)]- 2-[4-cyano-3- (trifluoromethyl)phe nyl]octahydro-4,7-</p>	<p>[M - H]<sup>-</sup> = 591.3</p>	483



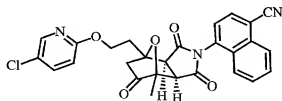
		dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindol-5-yl ester		
743		[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[Octahydro-5-hydroxy-4-methyl-7-[2-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.89 LCMS [M + H] <sup>+</sup> = 552.19	485, 486, 487 & 488
744		[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[7-[2-[[3-Chloro-5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.46 LCMS [M + H] <sup>+</sup> = 573.12	485, 486, 487 & 488
745		[3aS-(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )]-5-[7-[2-(3-Fluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.05 LCMS [M + H] <sup>+</sup> = 488.03	485, 486, 487 & 488

		4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile		
746		[3aS-(3α,4β,5β,7β,7α)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.98 LCMS [M + H] <sup>+</sup> = 538.23	485, 486, 487 & 488
751		[3aS-(3α,4β,5β,7β,7α)]-5-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.86 LCMS [M + H] <sup>+</sup> = 514.16	485, 486, 487 & 488

752		<p>[3aS-(3α,4β,5β,7β,7α)]-5-[7-[2-(4-Fluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile</p>	<p>3.02 LCMS [M + H]<sup>+</sup> = 488.2</p>	<p>485, 486, 487 &amp; 488</p>
753		<p>[3aS-(3α,4β,5β,7β,7α)]-5-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile</p>	<p>2.94 LCMS [M + H]<sup>+</sup> = 511.2</p>	<p>485, 486, 487 &amp; 488</p>

**Example 747**

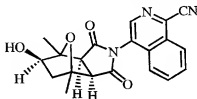
[3aR-(3α,4β,7β,7α)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (747)



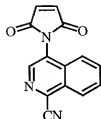
Dess-Martin periodinane (122 mg, 0.29 mmol, prepared as described in Ishiharaa, J., T. Fukuzakia, *et al. Tetrahedron Letters* **40**(10), 1907-1910 (1999)) was added to a solution of the compound **490A** (120 mg, 0.24 mmol) in dichloromethane (2.5 mL) under nitrogen and the mixture was stirred for 4h. The reaction was half concentrated under a stream of nitrogen and was applied on a flash cartridge (Jones 2 g) with celite on top and was eluted with chloroform:heptane (9:1) to chloroform:acetone (4:1) to give 148 mg of a still impure white solid. The solid was dissolved in dichloromethane (5 mL) and heptane (3 mL) and the precipitate was filtered over 1 g silica and was eluted with dichloromethane to chloroform:acetone (4:1). Fractions 3-9 (58.8 mg white solid) was almost pure and fractions 10-13 (68 mg white foam) were still impure. Fractions 3-9 were purified over silica (1 g) using heptane to heptane:ethyl acetate (1:1) as eluant to give 35.8 mg (30% yield) compound **747** as a white solid. Fractions 10-13 were purified by adding ~400 mg of silica to an excess solution of crude compound **747** in ethyl acetate and heptane and concentrating it. The silica was then put on top of a preconditioned (heptane) silica column (1 g) and was eluted with a gradient from heptane to heptane ethyl acetate (1:1) to give an additional 36.7 mg (31% yield) of compound **747** as a white solid. HPLC: 94% at 3.46 & 3.59 min (atropisomers, retention time) (YMC S5 ODS 4.6 X 50 mm, 4 mL min, 4 min gradient 100% A to 100% B (A: 10% methanol, 89.1% water, 0.1% TFA; B: 10% water, 89.1% methanol, 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 502.11 [M+H]<sup>+</sup>.

#### Example 748

(3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-isoquinolinecarbonitrile (748D)

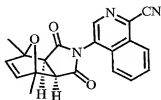


A. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-isoquinoline-1-carbonitrile (748A)



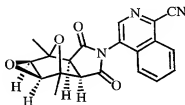
A mixture of compound **740D** (200 mg, 1.18 mmol) and maleic anhydride (470 mg, 4.7 mmol) in glacial acetic acid (5 mL) was heated to reflux for 4 hours. After removing the volatiles *in vacuo*, the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with saturated sodium bicarbonate solution (2 x 50 mL) and brine (50 mL). After drying over magnesium sulfate, the organic layer was filtered through a 1 x 5 cm plug of silica gel. The filtrate was concentrated to afford 263 mg (90%) of **748a** as an off-white solid. HPLC: 99% at 1.12 min (Phenomenex 5 micron ODS 4.6X30 mm, 10%-90% aqueous methanol over 2 minute gradient with 0.1% TFA, detecting at 254 nm). MS (ES):  $m/z$  250.2  $[M+H]^+$ .

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-isoquinolinecarboxitrile (748B)**



A mixture of compound **748A** (250 mg, 1 mmol) and 2,5-dimethylfuran (4 mL) was heated to 60°C for 2 h. At 15 min, the reaction mixture became homogeneous. A precipitate formed at 45 minutes. After cooling to 25°C, the reaction mixture was diluted with hexane and the filter cake was washed with ethyl ether:hexane, 1:1. Drying under high vacuum afforded 270 mg (78%) of compound **748B** as a light yellow solid.  $^1\text{H}$ NMR-400 MHz ( $\text{CDCl}_3$ ):  $\delta$  8.55 (s, 1H), 8.54 (m, 1H), 7.86 (m, 3H), 6.45 (s, 2H), 3.18 (s, 2H), 1.81 (s, 6H).

C. (1 $\alpha$ ,2 $\beta$ ,2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ ,6 $\alpha$ )-4-[Octahydro-2,6-dimethyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-1-isoquinolinecarbonitrile (**748C**)



*m*-CPBA, (70%, 110 mg, 0.45 mmol) was added to a solution of compound **748B** (100 mg, 0.29 mmol) in 3 mL of dichloromethane at 25°C. After 1 h, additional *m*-CPBA, (70%, 110 mg, 0.45 mmol) was added and the reaction mixture was stirred an additional 18 h. After partitioning the reaction mixture between ethyl acetate (30 mL) and water (30 mL), the organic layer was washed with saturated sodium bisulfite solution (30 mL), saturated sodium bicarbonate solution (2 x 30 mL) and brine (30 mL). The sample was dried over magnesium sulfate and concentration to yield 103 mg (98%) of compound **748C** as an off-white solid. HPLC: 99% at 1.09 & 1.22 min (atropisomers, retention time) (Phenomenex 5 micron ODS 4.6X30 mm, 10%-90% aqueous methanol over a 2 min gradient with 0.1% TFA, detecting at 254 nm). MS (ES): *m/z* 362.07 [*M*+H]<sup>+</sup>.

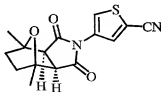
D. (3 $\alpha$ ,4 $\beta$ ,5 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-isoquinolinecarbonitrile (**748D**)

A 0.5 M solution of bis(cyclopentadienyl)titanium chloride in THF (1.2 mL, 0.6 mmol) was added dropwise over 20 min to a well stirred suspension of compound **748C** (103 mg, 0.29 mmol) in THF (2.5 mL) and 1,4-cyclohexadiene (1.2 mL) at 60°C. After stirring 1 h at 60°C, the reaction mixture was partitioned between 1N HCl (40 mL) and ethyl acetate (50 mL). The pH of the aqueous layer was adjusted to 7 with solid sodium bicarbonate. After extracting the aqueous with ethyl acetate, the combined organic layers

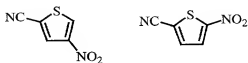
were dried over sodium sulfate. Decolorizing carbon (~1 g) was added and the mixture was allowed to stand for 18 h. Filtration and concentration of the filtrate *in vacuo* afforded a yellow oil that was chromatographed on a 2.5 x 15 cm silica gel column, using dichloro-methane:acetone, 6:4 as the mobile phase. Concentration of the product containing fractions *in vacuo* gave a partially purified residue that was subjected to preparative thin layer silica gel chromatography, using dichloromethane:acetone, 6:4 as the mobile phase. Extraction of the desired band with CH<sub>2</sub>Cl<sub>2</sub>, filtration and concentration of the filtrate *in vacuo* yielded 3 mg (31%) of compound **748D** as an off-white solid. HPLC conditions: 95% at 1.46 min (Phenomenex 5 micron ODS 4.6X30 mm, 10%-90% aqueous methanol over 2 minute gradient with 0.1% TFA, detecting at 254 nm). MS (ES): m/z 364.19 [M+H]<sup>+</sup>.

#### Example 749

(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-thiophenecarbonitrile (749C)



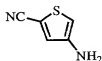
#### A. 2-Cyano-4-nitrothiophene (749Ai) & 2-Cyano-5-nitrothiophene (749Aii)



Fuming nitric acid (21 mL) was slowly added to glacial acetic acid (105 mL) and the mixture was then cooled in an ice-bath. 2-Cyanothiophene (7.98 g, 73.1 mmol) was dissolved in 20 mL of acetic anhydride and added dropwise to the above acid mixture such that the temperature did not exceed 25°C. Upon completion of the addition, the

reaction mixture was warmed to 22°C and stirred for 48 h. The reaction was poured over 400 mL of ice and extracted with 200 mL of diethylether. The ether layer was isolated, washed with water, followed by brine and dried over MgSO<sub>4</sub>. Filtration and concentration *in vacuo* gave a sticky, orange residue which was purified by column chromatography using 1:1 hexanes/ methylene chloride as the eluent to give 1.69 g (15%) of compound **749Ai** as a white solid and 1.71 g (15%) of compound **749Aii** as a yellow crystalline substance. . Compound **749Ai**: HPLC: 0.73 minutes (retention time) (Phenomenex column 30 x 4.6 mm eluting with 10-90% aqueous methanol over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm). Compound **749Aii**: HPLC: 99% at 0.89 minutes (retention time) (Phenomenex column 30 x 4.6 mm eluting with 10-90% aqueous methanol over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm).

**B. 4-Amino-2-cyanothiophene (749B)**



To a 100 mL 3-necked flask was added compound **749Ai** (1.42 g, 9.21 mmol) dissolved in ethyl acetate (20 mL) followed by a 10% acetic acid solution (20 mL). The biphasic mixture was heated to 65°C and then iron powder (2.95 g, 52.9 mmol) was added portion-wise over 5 minutes. After stirring for 1.5 h at 65°C, the reaction was filtered through a bed of Celite and the pad was washed with ethyl acetate. The organic layer was separated, washed with water (3 x 20 mL), brine and dried over MgSO<sub>4</sub>. Filtration and concentration *in vacuo* gave a dark amber residue which was purified by column chromatography using 30% diethyl ether / methylene chloride as the eluent to give 84 mg (73%) of compound **749B** as a brown solid. HPLC: 93.4% at 0.26 minutes (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

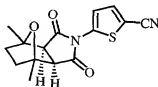


C. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-4-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-thiophenecarbonitrile (749C)

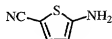
To a Pyrex tube was added compound **749B** (0.06 g, 0.5 mmol), toluene (1 mL), triethylamine (0.25 g, 0.35 mL, 2.5 mmol), MgSO<sub>4</sub> (0.15 g, 1.3 mmol), and compound **20A**. The tube was sealed with a teflon cap and heated overnight at 145°C. The reaction was cooled, diluted with methylene chloride and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography using 10% ether / methylene chloride as the eluent to give 14 mg (95%) of compound **749C** as a light yellow crystalline solid. HPLC: 94.6% at 2.6 minutes (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. MS (ES): *m/z* 303.05 [M+H]<sup>+</sup>.

Example 750

(3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-5-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-thiophenecarbonitrile (750B)



A. 5-Amino-2-cyanothiophene (750A)



To a 100 mL 3-necked flask was added compound **749Aii** (1.63 g, 10.1 mmol) dissolved in ethyl acetate (20 mL) followed by a 10% solution of acetic acid (20 mL). The biphasic mixture was heated to 65°C and then iron powder (2.95 g, 52.9 mmol) was added portion-wise over 5 minutes. After stirring for 1.5 h at 65°C, the reaction was filtered through a bed of Celite and the pad was washed with ethyl acetate. The organic layer was separated, washed with water (3 x 20 mL), brine and dried over MgSO<sub>4</sub>. Filtration and concentration *in vacuo* gave a dark amber residue which was purified by column chromatography using 10% diethyl ether / methylene chloride as the eluent to give 87 mg (66%) of compound **750A** as a brown solid. HPLC: 94.2% at 1.05 minutes (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

**B. (3 $\alpha$ ,4 $\beta$ ,7 $\beta$ ,7 $\alpha$ )-5-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-thiophenecarbonitrile (750B)**

To a Pyrex tube was added compound **750A** (0.06 g, 0.5 mmol), toluene (1 mL), triethylamine (0.25 g, 0.35 mL, 2.5 mmol), MgSO<sub>4</sub> (0.15 g, 1.3 mmol), and compound **20B**. The tube was sealed with a teflon cap and heated overnight at 145° C. The reaction was cooled, diluted with methylene chloride and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography using 10% ether/ methylene chloride as the eluent to yield 143 mg (96%) of compound **750B** as a light yellow crystalline solid. HPLC: 92.7% at 2.93 minutes (retention time) ( YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. MS (ES): m/z 303.21 [M+H]<sup>+</sup>.